SYNTHETIC ANALGESICS

PART IIA

MORPHINANS

ΒY

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PART IIB

6,7-BENZOMORPHANS

ΒY

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PERGAMON PRESS OXFORD • LONDON • EDINBURGH • NEW YORK PARIS • FRANKFURT

Pergamon Press Ltd., Headington Hill Hall, Oxford 4&5 Fitzroy Square, London W.1 Pergamon Press (Scotland) Ltd., 2&3 Teviot Place, Edinburgh 1 Pergamon Press Inc., 44–01 21st Street, Long Island City, New York 11101 Pergamon Press S.A.R.L., 24 rue des Écoles, Paris 5° Pergamon Press GmbH, Kaiserstrasse 75, Frankfurt-am-Main

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> > First Edition 1966

Library of Congress Catalog Card No. 59-13814

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PART IIA. Morphinans

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CHAPTER I

Chemistry of Morphinans

1. INTRODUCTION

Morphinans are members of a class of compounds possessing the main structural skeleton of morphine. The numbering system (1-17) and designation of the rings (A-D) adopted for these compounds are the same as used for morphine. The close relationship existing between these two classes of compounds is best seen by comparing their main structural features as given below.



Three condensed six-membered rings form the partially hydrogenated phenanthrene fragment, one of which is aromatic (A) while the two others (B and C) are alicyclic. As in decaline the fusion of rings B and C can either be *cis* or *trans* depending upon the configuration at C_{13} and C_{14} . Carbon 13 is quaternary and together with carbon 9 forms the junction with the heterocyclic ring (D). Although morphinan possesses three asymmetric carbon atoms, owing to the rigid structure of the molecule only two racemates are possible.

Morphinan could also be designated as a partially hydrogenated iminoethanophenanthrene or 2-aza-5,9-tetramethylene-6,7-benzo-bicyclo(1, 3, 3)nonene-(6)⁽¹⁾. This nomenclature, however, will not be used in this survey. Preference is given to a chemical designation derived from the skeleton "morphinan" adding the appropriate substituents and adhering to the numbering system already mentioned.

Originally, this class of compounds had been named "morphans", but, on the suggestion of ROBINSON⁽²⁾, this was modified to "morphinan" since the name morphan had already been adopted for another class of compounds⁽³⁾.

The chemistry of morphinan is very closely connected with that of morphine and starts from the elucidation of the structure of morphine by RO-BINSON⁽⁴⁾ and by SCHÖPF⁽⁵⁾ shortly afterwards. These two papers made pos-

sible the systematic study of the structure of the morphine alkaloids. By subjecting natural products to reactions which were either already well known or recently developed, many investigations were undertaken to confirm the morphine structure proposed by ROBINSON, and to find compounds of greater pharmacological value. The desirable effect of morphine on pain which sets in rapidly even when the drug is administered in small doses, is accompanied by a number of clinically undesirable side-effects. These side-effects, such as respiratory depression⁽⁶⁾ and development of tolerance which soon leads to addiction, limit its application.

The primary aim of the chemists in modifying the morphine molecule was to obtain analgesics without side-effects, especially without addictive properties. Although this has not yet been fully achieved, partial successes have been obtained, e.g. dihydrodesoxymorphine (desomorphine, Permonid^(R)) is about ten times more active than morphine⁽⁷⁾ and methyldihydromorphinone (Metopon^(R)) is distinctly less addictive than morphine⁽⁸⁻¹¹⁾.



These partial successes gave risc to the hope that the final goal, to obtain an analgesic without any addictive properties, might still be reached. This naturally stimulated chemical work in the morphine field and led to the understanding of numerous correlations between chemical structure and pharmacological activity^(7,12-14). Although we know now of a few exceptions, these generalizations may be summarized as follows^(15,16):

- (a) Replacement of the phenolic hydroxyl group of morphine by an ether group diminishes its analgesic effect considerably. On the other hand, esterification increases the analgesic and addictive properties.
- (b) Modification of the alcoholic hydroxyl group (by etherification, replacement by keto group, halogen etc.) increases the analgesic activity and the toxicity, at the same time diminishing the duration of the effect.
- (c) Opening the furan ring reduces the efficacy as well as the toxicity.
- (d) Substitution in the aromatic ring (A) lowers the analgesic activity.
- (e) Substitution in the alicyclic ring (C) does not basically modify the activity.
- (f) The formation of an N-oxide causes the activity to disappear; on quaternization of the tertiary amine a curare-like activity is observed.
- (g) Replacing the N-methyl grouping with N-alkyl or N-alkenyl groups leads to compounds with an antagonistic effect and, most important, the undesirable respiratory depression caused by morphine is significantly diminished⁽¹⁷⁾. There are well controlled studies showing that nalorphine retains some morphine-like respiratory depressant effect.

- (h) The tertiary character of the nitrogen is essential for the specific activity of morphine.
- (i) Opening the piperidine ring (morphimetine) destroys the analgesic activity completely.

2. SYNTHESIS OF ANALGESICS WITH MORPHINE-LIKE ACTIVITY

(a) Introduction

The elucidation of the structure of morphine and the knowledge of the relationship between chemical structure and physiological activity in morphine derivatives stimulated investigations directed towards the preparation of fragments of the complicated morphine molecule. It was hoped to obtain simpler compounds by total synthesis which would possess similar analgesic and antitussive properties but would be free of side-effects, especially of addictive properties. Following fragmentary efforts by various chemists around the turn of the century and during the next 25 years, synthetic work in the U.S.A. was supported mainly by the Committee on Drug Addiction of the National Research Council (USA) under the guidance of SMALL. EDDY *et al.* determined the pharmacological properties of these synthetic substances⁽⁷⁾.

Other research centres became involved later in these endeavours to "improve" morphine by synthetic studies with morphine fragments.

Table I summarizes these synthetic accomplishments. In most of the groups 1-13 some analgesic activity was found in a few of the representatives, but in spite of intensive work on groups which at first seemed very promising, no useful compounds were discovered. For details we recommend the excellent surveys of BERGEL and MORRISON⁽¹⁶⁾ and BECKETT⁽¹⁸⁾.

On the other hand, work on groups 14 and 15 was very successful. The first representative of group 14, pethidine⁽¹⁹⁾ (meperidine) proved to be of great importance and became the model for many other valuable compounds.

Group 15, methadone (Amidon^(R) and/or Polamidon^(R)) and analogues, is described in detail in the first volume of the series on *Synthetic Analgesics*⁽²⁰⁾.

In this second volume the results of chemical and pharmacological work with the morphinans 17 as well as the benzomorphans (group 16) shall be discussed.





TABLE I—continued

8.	Tetralones	(51) (51) (52) (53)
9.	Phenyl-amino- alkyl- cyclohexanes	(35) (54) (27) (55) (56)
10.	Phenyl- decahydro- isoquinolines	(57) (58)
11.	Diphenyl- alkylamines	$(54) \qquad (54) \qquad (54)$
12.	Phenyl-alkyl- amines	$(59) \qquad (60) \qquad (61)$
13.	Phenoxy-amino- alkyl-cyclo- hexanols	
14.	Phenyl- piperidines	
15.	Diphenyl- propyl amine s	(20)

TABLE I-continued

16.	Benzomorphans		Part IIB	
17.	Morphinans	N-R	Part IIA	

(b) Piperidine derivatives

In 1939, stimulated by synthetic work in the field of spasmolytics and the results of the pharmacological assay of the compounds obtained, EIS-LEB⁽⁶²⁻⁶⁴⁾ synthesized the ethyl ester of 1-methyl-4-phenylpiperidine-4-carboxylic acid (pethidine, meperidine, Dolantin^(R))⁽¹⁹⁾.



SCHAUMANN⁽⁶⁵⁾ showed that this compound was a spasmolytic in which atropine-like neurotropic and papaverine-like musculo-tropic activity occurred together for the first time. In addition, its analgesic effect far exceeded that of any of the synthetic compounds then known. The manifold chemical modifications of the meperidine molecule developed in various centres will be briefly outlined since this became in many respects the starting point for research work within the group of morphinans. Experience gained with the pethidine group led to the discovery of valuable compounds among the morphinans. In other cases, however, the same substituent did not cause analogous changes in the activity.

The central analgesic effect of pethidine is similar to, though weaker than, that of morphine. The side-effects are the same, though of different magnitude $^{(65)}$. This new analgesic produces addiction and checks abstinence symptoms after withdrawal of morphine $^{(66)}$. In small and intermediate doses it produces respiratory depression which can be checked, as with morphine, by *N*-allyl-normorphine or by (-)-3-hydroxy-*N*-allyl-morphinan $^{(67,68)}$. The morphine-like analgesic effect of pethidine led SCHAUMANN $^{(69)}$ to compare the chemical structure of the two groups of compounds. He concluded that 1-methyl-4-phenyl-piperidine is essential for analgesic activity in both groups. This conclusion greatly stimulated investigations directed towards the production of simpler fragments of the morphine molecule.



TABLE II

In the phenylpiperidine series, which was then studied on a large scale, further analgesics were developed. Besides pethidine, which is still of therapeutic importance in spite of competition from newer analgesics belonging to the same or different groups, a series of phenylpiperidine derivatives has been developed, the most important of which are given in Table II.

3. SYNTHESIS OF N-METHYL-MORPHINAN BY GREWE

(a) History

Once the structure of morphine had been elucidated, attempts to synthesize it began. As it may be considered both a phenanthrene and an isoquinoline derivative, different possibilities were available. In the very first attempts, the primary aim was to produce large fragments of the morphine molecule and thus obtain indications as to further steps towards its total synthesis. In addition, it was expected that these investigations would provide the final proof of ROBINSON's formula (1) for morphine, especially for the junction of the iminoethane bridge with the phenanthrene system. As the degradation of morphine alkaloids yielded mainly derivatives of phenanthrene or partially hydrogenated phenanthrene, it was natural that most synthetic attempts were directed towards the preparation of partially hydrogenated phenanthrenes carrying suitable substituents at the carbon atoms C_{13} and C_9 which, according to ROBINSON, form the junction with the heterocyclic ring.

FIESER et al.⁽⁸³⁻⁸⁵⁾ prepared a partially hydrogenated phenanthrene substituted at position 13 according to the following scheme:



By reacting 3,4-dihydro-naphthalene-1-carboxylic acid ethyl ester (5) with butadiene, they made a hexahydrophenanthrene-13-carboxylic acid ethyl ester (6) possessing the phenanthrene skeleton of morphine. The low reactivity of the ester grouping, however, precluded the completion of this synthesis of one of the known decomposition products of morphine^(86,87). Further experiments to synthesize such compounds by means of a diene synthesis failed⁽⁸⁸⁾.

An alternative method for making partially hydrogenated phenanthrenes (9) with a substituent at C_{13} was found by GHOSH and ROBINSON⁽⁸⁹⁾.



A simpler preparation of octahydrophenanthrenes was developed by BARDHAN and SENGUPTA⁽⁹⁰⁾ and BOGERT *et al.*^(91,92) They were able to show that cyclodehydration of 1-phenethyl-1-(or 2)-cyclohexanols produces octahydrophenanthrenes and that the same reaction with 1-phenethyl-2-methyl-1-(or 2)-cyclohexanol (10) leads to 13-methyloctahydrophenanthrene (11).



GREWE⁽⁹³⁾ followed a similar route to obtain partially hydrogenated phenanthrenes substituted at C_9 .



By reacting benzylmalonic ester (12) with α -chlorocyclohexanone (13), a mixture of the malonic ester derivative (14) and a lactone (15) was formed. Both yielded, on saponification and decarboxylation, the same keto acid (16) which was cyclized by heating with phosphoric acid to a hexahydro-phenan-threne-9-carboxylic acid (17).

GREWE⁽⁹⁴⁾ converted the keto acid (16) to phenanthrene derivatives substituted at position (9) and (13) in the following way:



By reacting methylmagnesium iodide with the keto acid (16) there was obtained, via the hydroxy acid (18) the lactone (19) which, when heated with phosphoric acid, cyclized to yield a mixture of two stereo-isomeric acids (20). The isomerism of the two acids (20) was established by the fact that on dehydrogenation both acids produced phenanthrene (21). This 13-methyl-5,6,7,8,9,10,13,14-octahydrophenanthrene-9-carboxylic acid (20) was the first phenanthrene derivative substituted at C atoms (9) and (13) to be synthesized.

It was then shown that the same reactions could also be applied to the synthesis of methyl or allyl substituted phenanthrenes. 1-phenethyl-cyclohexane derivatives in which the methyl group was replaced by acetic acid or by a dimethylaminoethyl side chain (22) yielded, in a similar cyclization reaction, octahydrophenanthrenes $(23)^{(95)}$ substituted at position (8).



The cyclization of 2-allyl-1-phenethyl-cyclohexanol (24) gave a phenanthrene derivative (25) with an angular allyl grouping, which, on ozonization yielded a substituted acetaldehyde (26).



Attempts to extend this method to 9-substituted octahydrophenanthreness failed; cyclization of the corresponding allylhydroxy esters (27) with phosphoric acid produced two carbocylic acids which did not have the anticipated structure.



By analogy $^{(96,97)}$ GREWE $^{(98)}$ considers the tetracyclic formulae (28) and (29) as possible structures for these two saturated acids.



Although it was clear that neither of the two compounds was suitable for further synthetic work, the structure of the carbotetracyclic acid (29) which showed surprising similarity to the desired heterocyclic ring system of morphine (1) led GREWE to speculations⁽¹⁾ which directed him in his further work on this problem. His ideas had some points in common with the hypotheses postulated in 1925 by ROBINSON⁽⁹⁹⁻¹⁰³⁾ on the biogenetic formation of morphine alkaloids. According to this hypothesis a benzyltetrahydroisoquinoline (e.g. 30) of the laudanosine type might be a precursor of these alkaloids in the plant (e.g. 31):



Similar biogenetic considerations and the relevant synthetic experiments are described by SCHÖPF⁽¹⁰⁴⁻¹⁰⁷⁾. The validity of these biogenetic hypotheses was not proved until 1960 when BATTERSBY *et al.*⁽¹⁰⁸⁻¹¹⁰⁾ were able to demonstrate the transformation of radioactive norlaudanosoline (32) into radioactive morphine (33) in the plant *Papaver somniferum*.



(b) The synthesis of N-methyl-morphinan

In analogy with the biogenetic assumptions of ROBINSON and SCHÖPF, GREWE chose as a possible precursor of the morphinans 1-benzyl-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (34) which carries the desired phencthyl-cyclohexene grouping suitable for the formation of a phenanthrene.



Under conditions resulting in cyclization with other hydrogenated phenanthrenes, this compound should yield the desired tetracyclic basic morphine skeleton (35) with an angular point of attachment of the heterocyclic ring. This consideration prompted GREWE to select this synthetic approach and led to his success. The intermediate product (34) was prepared by GREWE *et al.*^(1,111,112) via 5,6,7,8-tetrahydroisoquinoline (42) in the following way:</sup>



Ethyl cyclohexanone-carboxylate (37) is reacted with cyanoacetic ester to form the di-ester (38) which is saponified to 2-carboxy-cyclohexenyl-(1) acetic acid (39); the latter is cyclized with ammonia to yield 1,3-dihydroxy-5,6,7,8-tetrahydroisoquinoline (40). 5,6,7,8-tetrahydroisoquinoline (42) is obtained from (40) via the dichloroderivative (41). The iodomethylate (43) of the base (42) reacts with benzylmagnesium chloride to yield an unstable hexahydro base (44) which, opon hydrogenation, gives the desired 1-benzyl-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (34). On heating with concentrated phosphoric acid this yielded a stable well-crystallized base, m.p. 61 °C, for which the structure (35) (*N*-methyl-morphinan) was assumed and later proved by the HOFFMANN degradation:



The quaternary salt (45) is degraded to the hexahydrophenanthrene derivative (46). On dehydrogenation with palladium charcoal the side chain is split off and a good yield of phenanthrene (21) is obtained. This proves that the D ring of N-methyl-morphinan is attached to C_{13} and completes its structure determination.

By this elegant synthesis GREWE achieved for the first time the transformation postulated by ROBINSON and SCHÖPF of 1-benzylisoquinoline derivatives into compounds with the ring system of the morphine alkaloids.

A modification of this synthesis starting with 5-hydroxyisoquinoline was described some years later by KOELSCH and ALBERTSON⁽¹¹³⁾ who obtained *N*-methyl-morphinan by the following route:



The assumption that compounds of a morphine-like structure would also have pharmacological activities similar to morphine had already been proved for N-methyl-morphinan, the simplest representative of this class and which was shown to have analgesic properties of similar strength to morphine⁽¹⁾.

The discovery of the analgesic activity of *N*-methyl-morphinan stimulated pharmacological and technical interest in this group of compounds. Since *N*methyl-morphinan lacks any functional group of morphine, except the nitrogen grouping, it was hoped, by appropriate substitution of the morphinan molecule, to increase its activity and to obtain some differentiation in its pharmacological properties.

Interest was mainly focused on the 3-hydroxy derivative in which the hydroxy group is in an analogous position to that in morphine since EDDY *et al.*^(7,22) had already shown that 3-hydroxy-phenanthrene, unlike other hydroxy-phenanthrene compounds, possesses some analgesic activity.

4. Synthesis of 3-hydroxy-N-methyl-morphinan and analogous compounds

(a) From 5,6,7,8-tetrahydroisoquinoline

SCHNIDER *et al.* set out to produce derivatives of *N*-methyl-morphinan substituted with a hydroxyl group in the aromatic ring. As a first step they modified the synthesis of 5,6,7,8-tetrahydroisoquinoline (42) so as to make it practical for technical application⁽¹¹⁴⁾.



2-Hydroxymethylene-cyclohexanone (52) is aminated to the aminomethylene compound (53) and the latter condensed with malonic ester to yield 4carbethoxy-3-hydroxy-5,6,7,8-tetrahydroisoquinoline (54). After decarboxylation the resulting 3-hydroxy-tetrahydroisoquinoline (55) is treated with POCl₃ to yield the chloro derivative (56). Tetrahydroisoquinoline (42) is obtained on catalytic removal of chlorine. Independently of SCHNIDER⁽¹¹⁴⁾, SCHLITTLER and MERIAN⁽¹¹⁵⁾ prepared tetrahydroisoquinoline (42) soon afterwards in the same way.

SCHNIDER and GRÜSSNER⁽¹¹⁶⁾ achieved the synthesis of 3-hydroxy-N-methyl-morphinan (60) from 5,6,7,8-tetrahydroisoquinoline (42) by the following three methods:



(1) The bromomethylate (57) prepared from 5,6,7,8-tetrahydroisoquinoline (42) is transformed by means of *p*-methoxybenzylmagnesium chloride into the hexahydroisoquinoline derivative (58) which is then hydrogenated to 1-*p*-methoxy-benzyl-2-methyloctahydroisoquinoline (59). Heating with phosphoric acid yields a base melting at 251-253 °C which was shown to be 3-hydroxy-*N*-methyl-morphinan (60)⁽¹¹⁷⁾. Thus the cyclization is accompanied by splitting off the ether linkage. This method, although giving the desired 3-hydroxy-*N*-methyl-morphinan, was unsatisfactory as the yield in the reaction of tetrahydroisoquinoline bromomethylate (57) with *p*-methoxybenzylmagnesium chloride was poor. Even the use of excess of the Grignard reagent at low temperatures^(118,119) did not noticeably improve the yield.

(2) As the condensation of the bromomethylate (57) is more easily achieved with benzylmagnesium chloride than with *p*-methoxy-benzylmagnesium chloride, *N*-methyl-morphinan (35) was first prepared by the method outlined by GREWE *et al.*^(111,112).



The next step, nitration of *N*-methyl-morphinan, yielded two isomeric nitro compounds (61) which were separated by means of their picrates. The amino derivatives (62) obtained on catalytic hydrogenation were converted by diazotization into the corresponding hydroxy derivatives. One of the isomeric bases obtained was identical with 3-hydroxy-*N*-methyl-morphinan (60) synthesized according to method (1). The structure of 2-(or 4)-hydroxy-*N*-methyl-morphinan was proposed for the other and the 2-position of the hydroxy group was later proved ⁽¹²⁰⁾.

(3) The rather cumbersome separation of the nitromorphinans (61) led to the development of a further modification of the synthesis in which the nitration was transferred to an earlier stage and performed on 1-benzyl-2-methyloctahydroisoquinoline (34). Although nitro- and amino-benzyl-octahydroisoquinoline could not be cyclized, the treatment of 1-p-hydroxy-benzyl-2-methyloctahydroisoquinoline (64) with phosphoric acid yielded 3-hydroxy-N-methyl-morphinan (60).



Another way of making 3-hydroxy-N-methyl-morphinan from 5,6,7,8-tetrahydroisoquinoline (42) has been described by GREWE *et al.*⁽¹²¹⁾.



Heating 5,6,7,8-tetrahydroisoquinoline (42) with sodium amide yields the amino derivative (65) which is transformed into 1-bromo-5,6,7,8-tetrahydroisoquinoline (66). On treatment with butyl lithium the lithium derivative (67) is obtained. The latter reacts readily with *p*-methoxybenzaldehyde (anisaldehyde) to give the carbinol (68). This on treatment with hydrobromic acid is transformed into the bromide (69) and then reduced to compound (70). With methyliodide the latter gives the quaternary salt (71) which is hydrogenated to 1-*p*-methoxy-benzyl-2-methyloctahydroisoquinoline (59). Further treatment with hydrogen bromide causes cyclization to 3-hydroxy-*N*-methyl-morphinan (60) which is identical with the compound synthesized by SCHNIDER and GRÜSSNER⁽¹¹⁶⁾.

GREWE et al.⁽¹²¹⁾ were able to make 1-(3,4-dimethoxybenzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (72) in the same way from lithiumtetrahydroisoquinoline (67). This, when cyclized with concentrated hydrochloric acid, yielded small quantities of a compound identical in its physical and chemical properties with dl-tetrahydrodesoxycodeine (73).



In this way GREWE was able to confirm the morphine structure suggested by ROBINSON.

OCHIAI and IKEHARA⁽¹²²⁻¹²⁴⁾ elaborated a procedure similar to that of GREWE. They also found a new method of synthesizing 5,6,7,8-tetrahydroisoquinoline directly from isoquinoline and obtained morphinan in the following way:



Chlorotetrahydroisoquinoline (78) is condensed with the appropriate benzyl cyanide to yield 1-(α -cyanobenzyl)-tetrahydroisoquinoline (79). The latter is transformed by a series of unambiguous reactions to 1-(α -carbamoylbenzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (82) which, on treatment with phosphoric acid, yields N-methyl-morphinan. This procedure is also applicable to the preparation of 3-hydroxy-N-methyl-morphinan (R = OH) (83) and *dl*-tetrahydrodesoxycodeine (73).

(b) From cyclohexenylethylamine

As already indicated 3-hydroxy-*N*-methyl-morphinan possesses analgesic activity which is superior to that of morphine in its intensity as well as in its duration (125-127). The activity is, however, restricted to 3-hydroxy-*N*-methylmorphinan, its ether- and acylated derivatives. 2-hydroxy-*N*-methyl and 2,3-dihydroxy-*N*-methyl derivatives and 3-hydroxymorphinan non-substituted on the nitrogen show no pain-relieving properties.

The ever-increasing pharmacological interest in 3-hydroxy-*N*-methylmorphinan and its derivatives led SCHNIDER and HELLERBACH⁽¹²⁸⁾ to search for a synthesis of this compound which could be applied on a technical scale and which, in addition, would enable more extended work with this group to be carried out. 1-substituted 3,4-dihydroisoquinoline (85) can easily be prepared according to the reliable method of BISCHLER-NAPIERALSKI^(129,130) in which phenethylamides of the general formula (84) are cyclized to 3,4-dihydroisoquinolines by dehydration.



It now had to be determined whether this method of cyclodehydration could also be applied to the cyclohexenylethylamides of the formula (86). This would provide a simple method for the synthesis of the hexahydroisoquinolines (87).



It was first necessary to prepare the previously unknown β -cyclohexen-(1)yl-ethylamine (94) corresponding to phenethylamine; this was achieved as shown below:



Soon an even simpler method for the preparation of (94) was found. By condensing cyclohexanone (88) with cyanoacetic acid (95) cyclohexylidenecyanoacetic acid (96) is formed which, upon distillation, decarboxylates to yield cyclohexenylacetonitrile (97). This can be reduced to cyclohexenylethylamine (94) either with lithium aluminium hydride or even more easily catalytically in the presence of Raney cobalt.



Shortly afterwards it was discovered that this amine (94) which was easily obtainable in high yields could be used as starting material for the syntheses of several morphinans (ROCHE⁽¹²⁸⁾, GREWE⁽¹³¹⁾, HENECKA^(132,133), SASA-MOTO⁽¹³⁴⁾). In fact, SCHNIDER and HELLERBACH⁽¹²⁸⁾ found that cyclohexe-nylethylamides (e.g. 99) could easily be cyclized in good yields even when the reacting alicyclic double bond is not activated by any substituent⁽¹³⁵⁾.



Amides of the structure (99) were obtained by heating equimolar quantities of cyclohexenylethylamine (94) with substituted phenylacetic acids (98); these were cyclized by heating with $POCl_3$ to hexahydroisoquinolines (100). Catalytic hydrogenation in the presence of Raney nickel yielded the octahydro compound (101). This, on addition of formaldehyde and subsequent catalytic hydrogenation or on heating with formic acid gave the corresponding 1-benzyl-2-methyl-octahydroisoquinoline (103). On heating the latter with phosphoric acid cyclization to the corresponding substituted *N*-methylmorphinan (83) was achieved.

The intermediate products of this synthesis, which has been in use for several years on a technical scale (136), are all easily crystallizable stable compounds and are obtained in very good yields. The hexahydro base (100) undergoes an interesting modification when being distilled. In analogy with 3,4-dihydroisoquinoline it undergoes disproportionation to tetra- and octa-hydroisoquinoline derivatives. This is, however, of no importance as the base itself is not isolated during the technical process. *N*-Methyl-morphinan and its derivatives such as 3-hydroxy-, 2,3-dihydroxy- and 3-methoxy-4-hydroxy-

N-methyl-morphinan were synthesized by this method. The latter is identical with d_i -tetrahydrodesoxycodeine⁽¹²¹⁾.

2-Hydroxy-N-methyl-morphinan was obtained from 1-(m-methoxy-benzyl)-2-methyl-octahydroisoquinoline⁽¹²⁰⁾ and proved to be identical with the substance previously prepared by SCHNIDER and GRÜSSNER⁽¹¹⁶⁾.

SCHNIDER and HELLERBACH⁽¹³⁷⁾, by a slight variation of this procedure, synthesized octahydroisoquinolines via the intermediate cyclohexenylethyl methylamine.



Reaction of cyclohexenylethylamine (94) with methyl formate gives the formylamino compound (104) which, on reduction with LiAlH₄, yields cyclohexenylethylmethylamine (105). With the appropriately substituted phenylacetic acid chloride this amine yields amides of formula (106) which on cyclization give the benzylidene compounds $(107)^{(138)}$. After hydrogenating these substances to the known 1-benzyl-2-methyloctahydroisoquinolines (103), the latter can be cyclized to the corresponding *N*-methyl-morphinans (83). Cyclohexenylethylamine (94) and cyclohexenylethylmethylamine (105) were therefore also used in other classical methods for the synthesis of isoquinolines, e.g. by GREWE *et al.*⁽¹³¹⁾ in the method according to PICTET and SPENGLER⁽¹³⁹⁾.

Although cyclohexenylethylamine does not react with free phenylacetaldehydes, GREWE was able to carry out the desired reaction with cyclohexenylethylmethylamine (105) by a simplification of the procedure used for cyclohexenylethylamine.



With a phenylacetaldehyde of formula (108), the base (105) yields the enamine (109) which, depending on the cyclization conditions, yields either one or simultaneously three different amines (103), (110) and (111). The structure of these amines is elucidated by the fact that (110) and (111) are transformed by hydrochloric acid into the known 1-benzyl-2-methylocta-hydroisoquinoline (103). A variant of this synthesis was described by HE-NECKA^(132,133) who, contrary to GREWE *et al.*⁽¹³¹⁾ was able to condense cyclohexenylethylamine (94) with phenylacetaldehyde by using the bisulfite compound instead of the free aldehyde. This yields in analogy to GREWE's observations the 10-hydroxy derivative (112) which can be cyclized after *N*-methylation. HENECKA obtained the same compound on using a glycide ester instead of phenylacetaldehyde bisulfite for the reaction with cyclohexenylethylamine.



A further interesting procedure for the synthesis of 1-*p*-methoxy-benzyl-2methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (103), ($R = OCH_3$) was described by SUGASAWA and TACHIKAWA^(135,140) who obtained β -cyclohexa-1,4-dienylethylamine (113) from phenethylamine in very good yield by using the Birch reduction. They obtained 1-*p*-methoxybenzyl-2-methyloctahydroisoquinoline (103) from (113) according to the method described by SCHNIDER and HellerBACH⁽¹²⁸⁾.

(113)

When cyclization of mono- and dimethoxy-benzyl-*N*-methyloctahydroisoquinoline is carried out according to GREWE's method, the methyl groups are split off at the same time. With 1-(3,4-dimethoxybenzyl)-2-methyl-octahydroisoquinoline GREWE *et al.*⁽¹²¹⁾, as well as SCHNIDER and HELLERBACH⁽¹²⁸⁾, obtained a mixture of 2,3- and 3,4-dihydroxy-*N*-methyl-morphinan, the latter in very low yield. By an analogous reaction⁽¹²⁸⁾, SASAMOTO⁽¹³⁴⁾ prepared 1-(3,4-ethylenedioxybenzyl)-2-methyl-octahydroisoquinoline (114) starting from 3,4-ethylenedioxyphenylacetic acid and cyclohexenylethylamine.



On cyclization of (114) with phosphoric acid, the 2,3-ethylenedioxy compound (115) was obtained in about 30 per cent and 3,4-ethylenedioxy-*N*methyl-morphinan (116) in about 16 per cent yield. Apparently this kind of substitution allows cyclization to morphinans without cleavage of the ether linkages and therefore favours *ortho*-cyclization (16 per cent) as indicated in formula (116).

Attempts have also been made to obtain cyclohexenylethylamine, the starting material for the morphinan synthesis, by other routes. GREWE⁽¹⁴¹⁾ succeeded in synthesizing it according to the following reaction scheme:



When the BIRCH reduction of benzylcyanide is carried out with lithium in ethylamine⁽¹⁴²⁾, some cyclohexylethylamine is formed in addition to the main reaction product, cyclohexenylethylamine.

(c) From octahydrophenanthrene derivatives

GINSBURG and PAPPO⁽¹⁴³⁾ chose a new and original way, independent of other methods, for the synthesis of morphinans. They built up the morphine skeleton starting from the octahydrophenanthrene derivative (120).



Diketo-octahydrophenanthrene (120) was converted to the monoketal (121) which was transformed by treatment with amyl nitrite followed by hydrogenation into the 9-amino derivative (122). The latter was reacted with acetylglycolic acid chloride to yield (123). An attempt to make the diketal of this compound resulted in an unexpected cyclization to a tetracyclic compound. This compound had the structure (124) since on WOLFF-KISHNER reduction followed by treatment with LiAlH₄ it yielded an amine which, upon *N*-methylation, gave a substance identical with *N*-methyl-morphinan $(35)^{(26)}$. By utilizing this new method of cyclization, GINSBURG *et al.* synthesized dihydrothebainone from the appropriate starting materials. This was transformed into morphine ^(144,145) via 1-bromocodeinone by the method of GATES and TSCHUDI^(146,147).

(d) From β -tetralones

Another synthesis by BARLTROP and SAXTON⁽¹⁴⁸⁾ follows the reaction scheme shown below.



This synthesis gives, in small yield, a compound to which BARLTROP ascribesthe structure of 7-oxo-*N*-ethyl- $\Delta^{8(14)}$ -dehydromorphinan bromoethylate (131). This assumption is based on the similarity of the synthesis to the series of reactions used for preparing benzomorphan⁽³⁾ but, owing to lack of evidence, no rigorous proof exists.

5. Optically active 3-hydroxymorphinans

The morphine alkaloids obtained from natural products and their many transformation products, which have great therapeutic importance as analgcsics and antitussives, are optically active and all belong to the (-)-series.

The only exception is sinomenine $(132)^{(149)}$ which may be designated as the optical antipode of the yet unknown 7-methoxythebainone. Sinomenine was isolated from the Japanese plant Sinomenium acutum. It is *dextro*-rotatory and has no analgesic properties. In Japan sinomenine is used as an anti-rheumatic drug. By modification of the sinomenine structure some optical antipodes of morphine alkaloids or their derivatives such as *d*-tetrahydrodesoxycodeine, which are not found in nature, have been prepared and examined pharmacologically⁽¹⁵⁰⁻¹⁵²⁾.



With 3-hydroxy-*N*-methyl-morphinan the question arose as to whether the analgesic efficacy of the racemate is due to only one of the enantiomers, namely the one corresponding in its configuration to morphine.

Compounds with the skeleton of 3-hydroxy-N-methyl-morphinan (60) have three asymmetric carbon atoms (C₉, C₁₃ and C₁₄) and theoretically 8 optical isomers or 4 racemates should be possible. Since, however, the iminoethane bridge between the carbon atoms C₉ and C₁₃ can only adopt the *cis* configuration, the number of theoretically possible compounds is reduced to 4 optical antipodes or 2 racemates (133 + 134) differing in the configuration at the junction of rings B and C. The steric arrangement illustrated by formula (133) corresponds to 3-hydroxy-N-methyl-morphinan whereas formula (134) shows the configuration of isomorphinan.



(a) Resolution into optical antipodes

The resolution of the racemic 3-hydroxy-*N*-methyl-morphinan (60) into its optical antipodes was achieved with *d*-tartaric $\operatorname{acid}^{(153)}$. It was found that the tartrate of the (-)-antipode is the less soluble salt and crystallizes first.

This greatly facilitated the isolation of this enantiomer in an optically pure form.

In order to obtain an absolutely pure (+)-antipode, the resolution had to be carried out at an earlier stage of the synthesis with 1-(*p*-methoxybenzyl)- $^{-}$ -methyloctahydroisoquinoline (59) which has only one asymmetric carbon ...tom (C₁)⁽¹⁵⁴⁾.



This separation is achieved also with d-tartaric acid. In this case, the less soluble tartrate is formed by the base which, after the usual cyclization with phosphoric acid, yields (+)-3-hydroxy-*N*-methyl-morphinan. These two methods of resolution made possible the preparation of both enantiomers in optically pure form. This is important in view of their therapeutic use.

The assumption that the analgesic activity of the racemic 3-hydroxy-N-methyl-morphinan is the property of only one, the (-)-antipode, was confirmed with (-)-3-hydroxy-N-methylmorphinan tartrate (levorphanol, Dromoran^(R) – "Roche").

The further study of the optically active morphinans revealed that many representatives of the (-)-series are strong analgesics. Their activity can be increased or decreased by modifying the substituent on the nitrogen. The compounds of the (+)-series have, on the other hand, no analgesic properties; some of them possess, however, a distinct antitussive activity [(+)-3-incthoxy-*N*-methylmorphinan hydrobromide, dextromethorphan, Romilar^(R) – "Roche"] or, in higher dosage, a specific anti-rheumatic effect⁽¹⁵⁵⁾.

In addition to yielding optically pure (+)-3-hydroxy-*N*-methyl-morphinan the resolution prior to the final step of the synthesis also offered technical and economic advantages. There was a significant difference in the commercial demand for the products related to the two antipodes of 3-hydroxy-*N*methyl-morphinan, which does not lend itself to racemization owing to the rigidity of its skeleton. This prompted us to investigate the possibility of racemizing the unwanted antipode at an earlier stage.

After some attempts to racemize with platinum catalysts⁽¹⁵⁶⁾ a technically satisfactory solution of this problem was evolved. By heating optically active 1-benzyl-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinolines e.g. (59) in the presence of a specially prepared palladium-zinc-iron⁽¹⁵⁷⁾ or cobalt-copper⁽¹⁵⁸⁾ catalyst, the racemate is obtained and may be further used in the preparation of the desired antipode.

Further investigations with morphinans showed that the pharmacodynanic properties are not only dependent on the sterical configuration of the molecule but may also be modified by suitable substituents on the nitrogen atom. (-)-3-Hydroxy-N-allyl-morphinan (139) (levallorphan, Lorfan^(R)-

"Roche") showed especially interesting properties. It is a strong antagonist of the opiates; in low dosage it counteracts the side effects of the central analgesics and only in higher doses does it diminish the analgesic effect itself. Similar observations had already been made with N-allylnormorphine ^(159,160).

As attempts to resolve racemic 3-hydroxy-N-allyl-morphinan into its optical antipodes were unsuccessful, the (-)-enantiomer was obtained from (-)-3-hydroxy-N-methyl-morphinan by means of cyanogen bromide decomposition⁽¹⁵³⁾ according to VON BRAUN.



The 3-hydroxy group of (-)-3-hydroxy-N-methyl-morphinan is acetylated and the product (135) then transformed with cyanogen bromide into the cyanide (136). The latter is saponified to the desmethyl base (138) which on treatment with allylbromide gives the desired optically active N-allyl compound (139).

The technical synthesis could, however, be achieved by a simple route. The separation of the antipodes was carried out during an earlier stage by resolution of 1-*p*-hydroxybenzyl-1,2,3,4,5,6,7,8-octahydroisoquinoline $(140)^{(161)}$, obtained from the corresponding methoxy compound (101) by heating with potassium hydroxide. Only the tartrate of the (+)-hydroxy compound crystallized out from a methanolic solution of equimolar quantities of *d*-tartaric acid and the hydroxy base on cooling to 0°C. The concentrated mother liquors, on crystallization from water, yielded about an equal amount of the tartrate of the (-)-hydroxy base.



The free bases obtained from the two tartrates are optically pure. They are suitable starting materials for the synthesis of any pharmacologically interesting morphinans of the *laevo*-rotatory and *dextro*-rotatory series.

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Starting from the *dextro*-rotatory antipode, (-)-3-hydroxy-N-methyl and N-allyl-morphinan can be made in a technically simple way as follows:



Optically active 3-hydroxymorphinans (144) unsubstituted on the nitroen ⁽¹⁶¹⁾ may also be obtained by the following procedure:



The *dextro*-rotatory hydroxy base (140), for example, is transformed into the *laevo*-rotatory *N*-benzyl derivative (142). This is cyclized to (-)-3-hydroxy-*N*-benzylmorphinan (143) which yields (-)-3-hydroxymorphinan (144) on removal of the benzyl group by hydrogenolysis. (-)-3-Hydroxymorphinan (144) and its antipode which had been obtained in the same way were used as starting materials in the synthesis of other members of this class since any desired substituent on the nitrogen or oxygen atom could easily be introduced.

(b) The absolute configuration of the morphinans

The morphinans are similar to morphines in the structure of their basic skeleton, arrangement and fusion of the rings as well as in the position of the functional groups. The similarity of the parmacodynamic properties of (-)-3-hydroxy-N-methyl-morphinan and morphine suggests that the two compounds have the same absolute configuration. In this connection, we may mention the work of BECKETT^(162,163) on the structural specificity of analgesics; he assumes that the active enantiomers of the most important central analgesics have the same steric configuration.

In order to prove beyond doubt the steric structure of the morphinans, their absolute configuration was established in the following way⁽¹⁶⁴⁾:



By a route described by JEGER et al.⁽¹⁶⁵⁾, by means of which the cis-configuration had been established for rings B and C of morphine, (-)-3-

hydroxy-*N*-methylmorphinan (60) was subjected to a HOFFMANN degradation. The vinyl compound (150) was converted into the corresponding glycol (151) by treatment with osmium tetroxide. The glycol (151) was then transformed into the aldehyde and reduced by the WOLFF-KISHNER method. The oxidation of the reduction product with chromic acid led to the 10-keto derivative (154) which was subjected to ozonization. This reaction yielded (-)-cis-[2-methyl-2-carboxy-cyclohexyl-(1)]-acetic acid (155) which was identical with the dicarboxylic acid obtained by the decomposition of thebaine⁽¹⁶⁵⁾ and abietic acid⁽¹⁶⁶⁾.

In this way the relationship of the asymmetric carbon atoms 13 and 14 of the morphinans to those of morphine (156) was unambiguously established and their configuration correlated to glyceraldehyde. According to $\text{STORK}^{(167,168)}$ and RAPOPORT *et al.*⁽¹⁶⁹⁾ this proof also established the configuration at the asymmetric carbon atom 9 as shown in formula (133).

The (+)-3-hydroxy-*N*-methyl-morphinan (158) belonging to the enantiomeric series therefore has the same configuration as sinomenine $(157)^{(167,168)}$ at the carbon atoms 9, 13 and 14.



A direct transformation of sinomenine (157) into (+)-3-methoxy-*N*-methyl-morphinan (158) and of dihydrothebainone (163) into (-)-3-methoxy-*N*-methyl-morphinan (167) was achieved by SAWA *et al.*⁽¹⁷⁰⁾ in an original and elegant way, thus proving the correctness of the conclusions based on analogies and on degradative studies.





Sinomenine (157) is reduced by CLEMMENSEN's method to *d*-tetrahydrodesoxycodeine (159) and the latter is converted to the 4-phenylether derivative (160) by an ULLMANN reaction⁽¹⁷¹⁾ with bromobenzene in the presence of copper. On treatment with sodium in liquid ammonia this gives (+)-3methoxy-*N*-methyl-morphinan (161) in high yield. Similarly (-)-3-methoxy-*N*-methyl-morphinan (166) is obtained from dihydrothebainone- Δ^5 -enolether (162) or from dihydrothebainone (163) according to the following reaction scheme:



(166)

6. Isomorphinans

When carrying out the synthesis of morphine, GATES, WOODWARD *et al.*⁽¹⁷²⁾ also made morphinans differing in the steric structure of the molecule from the compounds previously described, in that the rings B and C (C_{13} and C_{14}) are in the *trans* position to each other (134).

The method discovered by GATES for making this series of compounds is
illustrated in the following scheme which shows the synthesis of both optical antipodes of 3-hydroxy-*N*-methyl-isomorphinan⁽¹⁷³⁾.



6-Methoxy-1,2-naphthoquinone (167, $R = CH_3$) prepared from 2,6-dihydroxynaphthalene by a three stage process, is transformed into the 4cyanomethyl derivative (169) which by a DIELS-ALDER reaction, yields the diketone (170). By reductive cyclization of this compound with a copper catalyst the keto-lactam (171) is obtained which is reduced to (172) by the HUANG-MINLON method. LiAlH₄ reduction followed by *N*-methylation leads to the methylether (174) of 3-hydroxy-*N*-methyl- \varDelta^6 -dehydroisomorphinan. Upon hydrogenation and *O*-demethylation this is transformed into 3-hydroxy-*N*methylisomorphinan (134) which is then resolved into its optical antipodes.

(-)-3-Hydroxy-N-methyl-isomorphinan(134, R = H) possesses 6 to 8 times the analgesic activity of morphine whereas its (+)-antipode is inactive in this respect.

(-)-3-Hydroxy- Δ^6 -dehydro-N-methyl-isomorphinan (174, R = H) also has analgesic activity though it is somewhat weaker than the hydrogenated derivative. On the other hand the 2-hydroxy-N-methyl-isomorphinen, which can be prepared in an analogous way, is completely inactive.

7. Structure of the by-products of the morphinan synthesis

On cyclization of 1-benzyloctahydroisoquinolines the desired N-substituted 3-hydroxymorphinans are obtained in about 60 per cent yield. The mother liquors yield by-products possessing the same empirical formula as the corresponding morphinans. One by-product (m.p. 209-210 °C) obtained consistently in a yield of 10 to 15 per cent during the preparation of (+)-3-hydroxy-*N*-methylmorphinan is (+)-6-methyl-10-hydroxy-1,2,3,3a,5,6,6a,7,11b,11c-decahydro-4*H*-dibenzo [*d*, *g*] quinoline (175). Its structure has been determined by HOFFMANN degradation⁽¹⁷⁴⁾. The 1-ethyl-6-methoxy-phenanthrene (177) which was obtained from (175) on decomposition to compound (176) followed by dehydrogenation was identical with the compound obtained by an unambiguous synthesis. This indicates the formation of these by-products due to a cyclization of benzyloctahydroisoquinolines as shown in formulae (59–175).



The structure of further by-products formed in the same cyclization reaction was elucidated by SAWA *et al.*⁽¹⁷⁵⁾. They isolated besides the apomorphine-like by-product (175) a stereo-isomer in about 3 per cent yield which melts at 206 °C. Another by-product formed in 3–5 per cent yield and melting at 173 °C was identified by SAWA *et al.*⁽¹⁷⁵⁾ as 3-hydroxy-*N*-methyl-isomorphinan (134). The apomorphine-like structure of the corresponding *N*-benzyl and *N*-allyl compounds isolated as by-products after analogous cyclizations of *N*-benzyl- or *N*-allyl-octahydroisoquinolines was also ascertaincd ⁽¹⁷⁴⁾.



The by-product (179) in the synthesis of (+)-3-hydroxy-N-benzylmorphinan yields on hydrogenolysis the secondary base (180). This, on N-allylation, yields the N-allyl compound (181) which is identical with the by-product produced by cyclization of 2-allyl-1-p-hydroxybenzyl-octahydroisoquinoline.

8. COMPILATION OF MORPHINAN DERIVATIVES

Even before its structure had been elucidated, attempts to modify the morphine molecule began. Acylation and alkylation of the hydroxy groups, oxidation and hydrogenation afforded a valuable insight into its chemical behaviour. In 1914 von BRAUN⁽¹⁷⁶⁾ found a way of demethylation and subsequent substitution of the morphine alkaloids with any desired radical. Soon POHL⁽¹⁶⁰⁾, followed by UNNA⁽¹⁵⁹⁾, demonstrated the interesting stimulating effect on respiration of *N*-allylnorcodeine and its antagonistic action to the specific activity of morphine. This led to the synthesis of further normorphines and norcodeines substituted at the nitrogen atom. CLARK *et al.*⁽¹⁷⁷⁾ found that some of the *N*-aralkyl compounds exhibited stronger analgesic activity than morphine.

In the morphinan series efforts were made to achieve a similar differentiation of the pharmacological properties.

Upon pharmacological investigation of a large number of substitution products, it was ascertained that alkylation and acylation of the 3-hydroxy group did not produce a fundamental change in the activity whereas the replacement of, for example, N-methyl by the N-allyl grouping^(153,161) led, as in the morphine series, to a reversal of the activity. N-alkyl^(116,161,180), N-alkenyl-⁽¹⁶¹⁾, N-alkynyl-⁽¹⁶¹⁾, N-aralkyl-⁽¹⁷³⁾ and N-heterocyclylalkyl-⁽¹⁷⁹⁾-morphinans were investigated in order to determine which compounds of this class were the best analgesics or the best antagonists respectively. The physical data of these compounds are listed in the following tables.

Two routes were followed in the preparation of these substances: either *N*-substitution of optically active 1-*p*-hydroxybenzyl-octahydroisoquinolines (140) followed by cyclization to the corresponding morphinans (183) or the *N*-substitution of racemic or optically active 3-hydroxymorphinans (144).



The esters of the 3-hydroxymorphinans were obtained by the reaction of tertiary bases with acid chlorides or acid anhydrides and the corresponding ethers by heating with phenyl-trialkyl(or alkenyl)-ammonium hydroxides.



R	R ₁	Base / Salts	m.p.	Formula	[¤] _D	Ref.
Н	Н	base	61°	C ₁₇ H ₂₃ N	dl†	111, 112, 128 132, 122, 123, 24, 26
H	Н	HCl	231–233°	$C_{17}H_{23}N \cdot HCl$	dl†	111, 112, 26
H	H	HBr	203–205°	$C_{17}H_{23}N \cdot HBr$	dl^{\dagger}	180
H	Н	H ₂ SO ₄	205°	$C_{17}H_{23}N \cdot H_2SO_4$	dl^{\dagger}	111, 112, 155
Н	Н	iodo- methylate	253°	C ₁₈ H ₂₆ NI	dl‡	111, 112
Н	Н	picrate	(186°) 207°		dl	121, 132
Н	Н	phosphate	241–243°		dl†	128
H	Н	d-tartrate	115–117°		()†	132
H	Н	base	33–35°		56†	132
H	NO ₂	picrate	248°		dl	116
H	NO ₂	HCl	268°	$C_{17}H_{22}O_2N_2 \cdot HCl$	dl‡	116
$NO_2(2)$	Н	picrate	207–209°		dl	
NO ₂ (2)	H	HCl	265°		dl ‡	116
H	NH ₂	base	114–115°		dl^{\pm}	116
NH ₂ (2)	Н	base	135–137°	$C_{17}H_{24}N_2$	dl^+	116
H	CH ₃ CONH	HBr	113–116°		dl^{\pm}	116
CH ₃ CONH(2)	Н	base	134–135°	$\mathrm{C_{19}H_{26}ON_2}$	dl‡	116

† Strong analgesic activity
* Weak or no analgesic activity

see pharmocological part.

TABLE III—continued

R	R ₁	Base / Salts	m.p.	Formula	[α] _D	Ref.	
Н	НО	base	251–253°	C ₁₇ H ₂₃ ON	dl†	116, 128, 121, 122, 123, 124, 133, 140, 132	
H	но	HBr	193–195°	$C_{17}H_{23}ON \cdot HBr$	dl†	116, 128, 121	
H	НО	HCl	176–178°	$C_{17}H_{23}ON \cdot HCl$	dl^{\dagger}	116	Q
H	НО	H ₂ SO ₄	212–214°	$C_{17}H_{23}ON \cdot H_2SO_4$	dl^{\dagger}	116	H
H	НО	base (iso?)	234–237°	17 25 2 4	dl^{\dagger}	128	ΞM
H	но	HBr (iso?)	240–243°		dl^{\dagger}	128	SI
Н	но	d-tartrate	147°		dl^{\pm}	128	ΤR
н	но	bromo- methylate	260–262°	C ₁₈ H ₂₆ ONBr	dl^{\pm}	180	CY O
н	но	chloro- benzylate	211–212°	C24H30ONCl	dl^{\pm}	180	F M
HO(2)	Н	base	93–95°	C ₁₇ H ₂₃ ON	dl^{+}	116	OF TO
HO(2)	Н	HBr	154–156°	$C_{17}H_{23}ON \cdot HBr$	dl^{\pm}	116	F
HO(2)	Н	bromo- methylate	145–148°	C ₁₈ H ₂₆ ONBr	dl^{\pm}	180	HIN,
Н	CH ₃ O	base	81–83°	C ₁₈ H ₂₅ ON	dl^{\dagger}	116, 128, 121, 132	ANS
Н	CH ₃ O	HBr	91–93°	$C_{18}H_{25}ON \cdot HBr$	dl^{\dagger}	116, 128	
Н	CH ₃ O	picrate	168°	10 10	dĺ	121, 132, 113	
Н	CH ₃ O	iodo-	250-251°	C ₁₉ H ₂₈ ONI	dl^{\pm}	180	
	-	methylate					
H	C ₂ H ₅ O	HBr	212–213°	$C_{19}H_{27}ON \cdot HBr$	dl†	180	
H	$CH_3CH_2CH_2O$	HBr	98°	$C_{20}H_{29}ON \cdot HBr$	dl^{\pm}	180	
H	$CH_2 = CHCH_2O$	HBr	76–77°	$C_{20}H_{27}ON \cdot HBr$	dl‡	128	
H	C ₆ H ₅ CH ₂ O	HBr	223–224°	$C_{24}H_{29}ON \cdot HBr$	dl^{\pm}	128	
		l					37

TABLE III -- continued

R	R ₁	Base / Salts	m.p.	Formula	[α] _D	Ref.
Н	CH ₃ COO	HBr	210–212°	C ₁₉ H ₂₅ O ₂ N · HBr	dl†	116
н	H ₂ N-COO	HCI	198–200°	$\mathrm{C_{24}H_{28}O_2N_2} \cdot \mathrm{HCl}$	dl+	180
н	(CH ₃) ₂ NCOO	bromo- methylate	250–252°	$C_{21}H_{31}O_2N_2Br$	dl‡	180
(CH ₃) ₂ NCOO(2)	Н	bromo- methylate	259–261°	$C_{21}H_{31}O_2N_2Br$	dl +	180
H	Cl	HBr	254–256°	$C_{17}H_{22}NCl \cdot HBr$	dl+	180
(2)O(CH ₂) ₅ O(2)	Н	bromo- methylate	210°	$C_{41}H_{60}O_2N_2Br_2$	dl+	180
Br(2)	НО	base	190°		dl‡	121
Br(2)	НО	HBr	236–243°		dl^{\pm}	121
Br(2)	НО	picrate	145°		dl^{\pm}	121
Br(2)	CH ₃ O	base	152·5°		dl^{\pm}	121
Br(2)	CH ₃ O	picrate	238–239°		dl	121
I(2)	НО	base	196°	$C_{17}H_{22}ONI$	dl^{\pm}	121
I(2)	HO	HCl	223–224°	$C_{17}H_{22}ONI \cdot HCl$	dl^{\ddagger}	121
I(2)	НО	HBr	223°	$C_{17}H_{22}ONI \cdot HBr$	dl	121
I(2)	но	picrate	162-168°		dl	121
I(2)	CH ₃ O	base	178·5°	C ₁₈ H ₂₄ ONI	dl^{\pm}	121
I(2)	CH ₃ O	picrate	238°		dl	121
HO(2)	НО	base	246–247°; 139°	$C_{17}H_{23}O_2N$	dl‡	128, 121
HO(2)	НО	salicylate	176–180°		dl	128
HO(2)	НО	HBr	248-250°	$C_{17}H_{23}O_2N \cdot HBr$	dl^{\pm}	128, 121
HO(2)	НО	iodo- methylate	242°	C ₁₈ H ₂₆ O ₂ NI	dl	180
HO(2)	CH ₃ O	base	187–188°	$C_{18}H_{25}O_2N$	dl	121

R	R1	Base / Salts	m.p.	Formula	[α] _D	Ref.
CH ₃ O(2)	CH ₃ O	picrate	211°	C ₂₅ H ₃₀ N ₄ O ₉	dl	121, 128
CH ₃ O(2)	CH ₃ O	iodo- methylate	237°		dl	121
HO(4)	CH ₃ O	base	127–130°	$C_{18}H_{25}NO_2$	dl	121, 128, 122, 123, 124
HO(4)	CH ₃ O	<i>d</i> -tartrate	110°		()	121
$CH_{3}(1)$	но	HC1	276–277°	$C_{18}H_{25}ON \cdot HCl$	dl†	180
$CH_3(2)$	НО	HCl	145–148°	$C_{18}H_{25}ON \cdot HCl$	dl‡	180
$CH_3(2)$	CH ₃ O	HBr	235–238°	$C_{19}H_{27}ON \cdot HBr$	dl‡	180
$H_2N(2)$	но	HBr	242–245°	$C_{17}H_{24}ON_2 \cdot HBr$	dl	180
$(C_2H_5)_2N \cdot CH_2(2)$	но	HCl	251-252°	$C_{22}H_{34}ON_2 \cdot HCl$	dl^{\pm}	180
Br(4)Br(2)	НО	HBr	215–217°		dl	121
Br(2)Br(4)	НО	base	210/152 to 153°	C ₁₇ H ₂₁ NOBr ₂	dl	121
Br(2)Br(4)	но	picrate	193°		dl	121
Br(2)Br(4)	CH ₃ O	picrate	190°		dl	121
$CH_{2}(2)$	CH ₃	HBr	217–218°		dl*	180
H	HO	base	198–199°	$C_{17}H_{23}ON$	- 56†	153
H	НО	d-tartrate	206–208°	$C_{17}H_{23}ON \cdot C_4H_6O_6$	- 13.8†	153
Н	НО	d-tartrate	183–185°	$C_{17}H_{23}ON \cdot C_4H_6O_6$	+ 34.6+	153
Н	НО	base	198–199°	$C_{17}H_{23}ON$	+ 56-3+	153
н	но	phenyl- butyrate	162–164°		(—)†	153
Н	НО	mandelate	190–191°		()†	153
Н	но	benzoate	185°	}	()†	153
н	но	cinnamate	100-101°		()†	153
н	но	gentisinate	156–159°		()†	153
н	НО	salicylate	220°		(+)+	153

TABLE III—continued

TABLE III—continued

R	R ₁	Base / Salts	m.p.	Formula	[α] _D	Ref.
н	НО	d-camphor-	237-240°		()	153
Н	НО	<i>d</i> -camphor- sulfonate	231–232°		(+)	153
Н	НО	2,6-dihy- droxy- benzoate	221–223°		(+)	180
н	но	iodo- methylate	280–281°	C ₁₈ H ₂₆ ONI	+23.9	180
Н	НО	N-oxide	205–208°	$C_{17}H_{23}O_2N$	+23.75+	180
H	НО	N-oxide	220°	$C_{17}H_{23}O_2N$	25·9‡	180
H	CH ₃ O	base	109–111°	C ₁₈ H ₂₅ ON	49·3†	153
Н	CH₃O	d-tartrate	156–157°	$C_{18}H_{25}ON \cdot C_4H_6O_6$	— 11·6†	153
H	CH ₃ O	HBr	124–126°	$C_{18}H_{25}ON \cdot HBr$	- 26·3†	153
Н	CH ₃ O	r hosphate	199–200°		(—)†	153
H	CH ₃ O	base	109–111°	$C_{18}H_{25}ON$	+49.6*	153
H	CH ₃ O	d-tartrate	195–196°	$C_{18}H_{25}ON \cdot C_4H_6O_6$	+30.6+	153
H	CH ₃ O	HBr	124–126°	$C_{18}H_{25}ON \cdot HBr$	$+25.6^{+}$	153
H	CH ₃ O	phosphate	199–200°		(+)	153
Н	CH ₃ O	phenol- phtalinate	274–276°		(+)	153
H	CH ₃ O	salicylate	97–100°		(+)	180
H	CH ₃ O	N-oxideHBr	195°	$C_{18}H_{25}O_2N \cdot HBr$	+16.3	180
H	C ₂ H ₅ O	phosphate	227–228°	$C_{19}H_{27}ON \cdot H_3PO_4$	- 28.16†	153
H	C ₂ H ₅ O	phosphate	227–228°	$C_{19}H_{27}ON \cdot H_3PO_4$	$+28.66 \pm$	153
H	CH ₃ CH ₂ CH ₂ O	d-tartrate	95-102°	$\mathrm{C_{20}H_{29}ON}\cdot\mathrm{C_4H_6O_6}$	9·16+	153
H	CH ₃ CH ₂ CH ₂ O	d-tartrate	98–105°	$C_{20}H_{29}ON \cdot C_4H_6O_6$	+ 32·16+	153
Н	$CH_2 = CHCH_2O$	HBr	167–168°	$C_{20}H_{28}ON \cdot HBr$	— 32·2†	153

TABLE III—continued

R	R ₁	Base / Salts	m.p.	Formula	[¤] _D	Ref.
H H H H H H H H H H H H	$CH_2 = CHCH_2O$ $(C_2H_5)_2N \cdot CH_2CH_2O$ CH_3COO CH_3COO CH_3CH_2COO CH_3CH_2COO $CH_3(CH_2)_{14}COO$ $CH_3(CH_2)_{14}COO$ C_6H_5COO C_6H_5COO C_6H_5COO $(CH_3)NCOO$	HBr base d-tartrate HBr d-tartrate d-tartrate d-tartrate d-tartrate d-tartrate d-tartrate HBr base	$\begin{array}{c} 167168^\circ\\ b_{0\cdot02}173^\circ\\ 115117^\circ\\ 160161^\circ\\ 155156^\circ\\ 106108^\circ\\ 106108^\circ\\ 144145^\circ\\ 173174^\circ\\ 224225^\circ\\ 218219^\circ\\ 0il \end{array}$	$C_{20}H_{28}ON \cdot HBr$ $C_{23}H_{36}ON_{2}$ $C_{19}H_{25}O_{2}N \cdot C_{4}H_{6}$ $C_{19}H_{25}O_{2}N \cdot HBr$ $C_{20}H_{27}O_{2}N \cdot C_{4}H_{6}O_{6}$ $C_{20}H_{27}O_{2}N \cdot C_{4}H_{6}O_{6}$ $C_{33}H_{53}O_{2}N \cdot C_{4}H_{6}O_{6}$ $C_{24}H_{27}O_{2}N \cdot C_{4}H_{6}O_{6}$ $C_{24}H_{27}O_{2}N \cdot C_{4}H_{6}O_{6}$ $C_{24}H_{27}O_{2}N \cdot C_{4}H_{6}O_{6}$ $C_{24}H_{27}O_{2}N \cdot MBr$ $C_{24}H_{27}O_{2}N \cdot HBr$	+32.8* (+)* -6.5† +18.6* -7.17† +25.2* -4.13 +18.0 -21.6 +35.5 +35.6 +43	153 180 153 153 153 153 153 153 153 153 153 153
н		d-tartrate	110–111°	$C_{20}H_{26}O_2N_2 \cdot C_4H_6O_6$	- 19.8†	180
$\begin{array}{c} Br(2)\\ Br(2)\\ CH_3(1)\\ CH_3(2)\\ CH_3(2)\\ CH_3(2)\\ CH_3(2)\\ CH_3(2)\\ CH_2=CH-CH_2(2)\\ CH_2=CH-CH_2(2)\\ CH_2=CH-CH_2(2)\\ CH_2=CH-CH_2(2)\\ \end{array}$	HO CH_3O HO HO HO HO CH_3O CH_3O HO HO HO HO	HBr HBr HCl HCl HCl HCl d-tartrate d-tartrate HCl citrate citrate	185–187° 231–233° 312–313° 171–173° 170° 199–200° 166–168° 280–282° 143–145°	$\begin{array}{c} C_{17}H_{22}ONBr \cdot HBr\\ C_{18}H_{24}ONBr \cdot HBr\\ C_{18}H_{25}ON \cdot HCl\\ C_{18}H_{25}ON \cdot HCl\\ C_{18}H_{25}ON \cdot HCl\\ C_{18}H_{25}ON \cdot HCl\\ C_{19}H_{27}ON \cdot C_{4}H_{6}O_{6}\\ C_{19}H_{27}ON \cdot C_{4}H_{6}O_{6}\\ C_{20}H_{27}ON \cdot HCl\\ C_{20}H_{27}ON \cdot C_{6}H_{8}O_{7}\\ C_{20}H_{27}ON \cdot C_{6}H_{8}O_{7}\\ \end{array}$	$(+) + 13 \cdot 8 - 89 \dagger + 89 \cdot 33 = -20 \cdot 6 = +21 \cdot 2 = -12 \cdot 5 = (+) = -52 \cdot 51 = -52 \cdot 51 = -21 \cdot 71 \dagger +21 \cdot 76$	180 180

TABLE III— continued	

R	R ₁	Base / Salts	m.p.	Formula	[α] _D	Ref.
CH ₃ (1)	HO, HO(4)	HBr	300–305°		dl, α^{\pm}	133
CH ₃ (1)	HO, HO(4)	HBr	310°		dl, β^{\pm}	133
$CH_3(1)$	$CH_{3}COO, CH_{3}COO(4)$	base	172–174°		dl, α^{\pm}	133
CH ₃ (1)	$CH_{3}COO, CH_{3}COO(4)$	base	168°		dl, β^{\pm}	133
CH ₃ (1)	$CH_{3}COO, CH_{3}COO(4)$	HCl	300–305°		dl, α^{\pm}	133
CH ₃ (1)	$CH_{3}COO, CH_{3}COO(4)$	HCl	291–293°		dl, β^{\pm}	133
H	HO, $CH_3(6)$	base	272–275°		dl, α^{\dagger}	133
н	HO, $CH_3(6)$	base	234–236°		dl, β^{\ddagger}	133
H	CH ₃ O	base	75–76°		dl, α	133
н	CH ₃ COO	base	112–113°		dl, α	133
H	HO, CH ₃ (6)	base	226–228°		-69, α†	133
H	HO, CH ₃ (6)	base	226–228°		$+71, \alpha$	133
H	CH_3O , $CH_3(6)$	base	80°		$-62.2, \alpha^{+}$	133
Н	$CH_3O, CH_3(6)$	base	78–80°		$+60.8, \alpha$	133
н	HO, CH ₃ (15)	HCl	177–178°	$C_{18}H_{25}ON \cdot HCl$	dl ‡	180
Н	CH ₃ O, 10-oxo	base	189–190°	$C_{18}H_{23}O_2N$		295
н	CH_3O , 10-oxo	iodo-	243–245°	$C_{19}H_{26}O_2NI$	-3	295
		methylate				
Н	CH ₃ O, 10-oxo	oxime	265°	$C_{18}H_{24}O_2N_2$	()	295
H	CH ₃ O, 10-oxo	base	188–189°	$C_{18}H_{23}O_2N$	+140	295
H	CH_3O , 10-hydroxy	base	136°	$C_{18}H_{25}O_2N$	- 18	295
H	CH_3O , 10-hydroxy	base		$C_{18}H_{25}O_2N$	+18	295
н	CH_3O , 10-hydroxy	HCl	180–182°	$C_{18}H_{25}O_2N \cdot HCl$	+14	295
Н	CH_3O , 10-hydroxy	HCl	180–181°	$C_{18}H_{25}O_2N \cdot HCl$	- 14	295



R		Base / Salts	m.p.	Formula	[α] _D	Ref.
		picrate	210-212°		dl	172, 111, 112
Н		base	oil	C ₁₇ H ₂₃ N	dl^{\dagger}	172
н		iodo-	233–236°	$C_{18}H_{26}NI$	dl	172
		methylate				
$CH_{3}O$	Δ° -dehydro	base	oil	$C_{18}H_{23}ON$	dl	173
CH₃O	Δ^6 -dehydro	picrate	224–225°	$C_{24}H_{26}O_8N_4$	dl	173
CH₃O	⊿ ⁶ -dehydro	iodo- methylate	198–200°	C ₁₉ H ₂₆ ONI	dl	173
CH ₂ O	6.7-dimethyl- Δ^6 -dehydro	base	oil	C20H27ON	dl	173
CH ₂ O	6.7-dimethyl- 1^{6} -dehydro	nicrate	222-224°	C26H30O8N4	dl	173
HO	Δ^{6} -dehydro	base	221-223°	$C_{17}H_{21}ON$	dl	173
но	Δ^6 -dehydro	iodo-	220–222°	$C_{18}H_{24}ONI$	dl	173
		methylate				
CH ₃ O	Δ^6 -dehydro-10,16-dioxo		167-170°	$C_{18}H_{19}O_{3}N$	dl	173
CH ₃ O	6,7-dimethyl-⊿ ⁶ -dehydro-10,16- dioxo		179–181°	$C_{20}H_{23}O_3N$	dl	173
НО	6,7-dimethyl- Δ^6 -dehydro	base	184–186° 164–166°	C ₁₉ H ₂₅ ON	dl†	173
НО	6,7-dimethyl-⊿ ⁶ -dehydro	iodo- methylate	217–219°	C ₂₀ H ₂₈ ONI	dl	173
HO		base	217-218°	C ₁₇ H ₂₃ ON	dl	173
НО		iodo- methylate	224–225°	$C_{18}H_{26}ONI$		173

† Strong analgesic activity # Weak or no analgesic activity see pharmacological part.

TABLE IV—continued

R		Base / Salts	m.p.	Formula	[α] _D	Ref.
CH ₃ O	⊿ ⁶ -dehydro	dibenzoyl- L(+)-tartrate	175°	$C_{18}H_{23}ON \cdot C_{18}H_{14}O_8$	8.8	173
CH ₃ O	⊿ ⁶ -dehydro	base	6162°	$C_{18}H_{23}ON$	+33.9	173
CH ₃ O	Δ^{6} -dehydro	picrate	240·5–242°	$C_{24}H_{26}O_8N_4$		173
CH ₃ O	⊿ ⁶ -dehydro	dibenzoyl-	174–175°	$C_{18}H_{23}ON \cdot C_{18}H_{14}O_8$	+6.5	173
CULO	16 dehadre	basa	61.5 620	C H ON	24.2	172
	16 debudro	Dase	01.3 - 03 $230 - 241^{\circ}$	$C_{18}\Pi_{23}ON$	34.3	173
	16 debudro	hasa	166 1679	$C_{24}\Pi_{26}O_8\Pi_4$	1 22.4=	173
	16 debudro	base	166 1670	$C_{17}H_{21}ON$	+ 23.4 .	173
		Dase	100-107 117 1100	$C_{17}H_{21}ON$	- 20.0 1	173
	16-0X0-		100/2409	$C_{17}H_{21}ON$	ai 11	173
NO_2	16-0x0-		190/240	$C_{17}H_{20}O_{3}N_{2}$		173
$NO_2(2)$	16-0x0-		188-189	$C_{17}H_{20}O_{3}N_{2}$	ai	1/3
$NU_2(1)$	16-0x0-	hasa	227-229	$C_{17}\Pi_{20}O_{3}N_{2}$		1/3
$N\Pi_2$	16-0X0-	base	207-211	$C_{17}H_{22}ON_2$		1/3
$NH_2(2)$	16-0X0-	Dase	188-190-	$C_{17}H_{22}ON_2$	ai	1/3
$NH_2(1)$	16-0X0-	base	229-231	$C_{17}H_{22}ON_2$	al	173
NH ₂		base	124-124.5°	$C_{17}H_{24}N_2$	dl	173
$NH_2(2)$		base	125-127	$C_{17}H_{24}N_2$	dl	173
$NH_2(2)$		picrate	237-238	$C_{23}H_{27}O_7N_5$	dl	173
$NH_2(1)$		picrate	197–200°	$C_{23}H_{27}O_7N_5$	dl	173
HO(2)		base	181–182·5°	$C_{27}H_{23}ON$	dl^{\pm}	173
HO(1)		base	201–202°	$C_{27}H_{23}ON$	dl^{\pm}	173
HO		dibenzoyl-	156–158°	$C_{17}H_{23}ON \cdot C_{18}H_{14}O_8$	46.6	173
		L(+)-tartrate				
НО		dibenzoyl-	156–158°	$C_{17}H_{23}ON \cdot C_{18}H_{14}O_8$	+ 47•9	173
НО		base	171–172·5°	C ₁₇ H ₂₃ ON	+ 55•5*	173

R		Base / Salts	m.p.	Formula	[α] _D	Ref.
НО		iodo- methylate	255–258°	C ₁₈ H ₂₆ ONI	+	173
HO		hydriodide	154–156°	C ₁₇ H ₂₃ ON · HI	+	173
HO		base	171–173°	$C_{17}H_{23}ON$	— 53·8†	173
НО		iodo- methvlate	255–257°	C ₁₈ H ₂₆ ONI		173
НО		hydriodide	153–156°	C17H23ON · HI		173
CH ₃ O	N-desmethyl-⊿ ⁶ -dehydro-10,16- dioxo	•	266–267·5°	C ₁₇ H ₁₇ O ₃ N	dl	173
CH ₃ O	N-desmethyl-6,7-dimethyl-∆ ⁶ - dehydro-10,16-dioxo		274–276·5°	C ₁₉ H ₂₁ O ₃ N	dl	173
CH ₃ O	<i>N</i> -desmethyl- Δ^6 -dehydro-16-oxo		196–197°	$C_{17}H_{19}O_2N$	dl	173
CH ₃ O	N-desmethyl-6,7-dimethyl-∆ ⁶ - dehydro-16-oxo		215–219°	$C_{19}H_{23}O_2N$	dl	173
Н	N-desmethyl-⊿ ⁶ -dehydro-16-oxo		240–242°	C ₁₆ H ₁₇ ON	dl	173
H	N-desmethyl-16-oxo		208–210°		dl	173
НО	N-desmethyl-⊿ ⁶ -dehydro-10,16- dioxo		311–314°	$C_{16}H_{15}O_{3}N$	dl	173
но	<i>N</i> -desmethyl-6,7-dimethyl- Δ^6 - dehydro-10,16-dioxo		353–356°	$C_{18}H_{19}O_3N$	dl	173
HO	<i>N</i> -desmethyl- Δ^6 -dehydro-16-oxo		266–268°	$C_{16}H_{17}O_2N$	dl	173
НО	N-desmethyl-6,7-dimethyl-⊿ ⁶ - dehydro-16-oxo		245–247·5°	$C_{18}H_{21}O_2N$	dl	173

TABLE IV—continued



R	R ₁	Base / Salts	m.p.	Formula	[¤] _D	Ref.
Н	CH ₂ CH ₂	HBr	244-245°	C18HarN · HBr	dl^{\dagger}	180
HO	CH ₂ CH ₂	HBr	268-269°	CtoHorON · HBr	dl^{\pm}	116
HO	CH ₂ CH ₂	HBr	319-320°	$C_{18}H_{25}ON \cdot HBr$	-41.2†	180
HO(2)	CH ₂ CH ₂	HBr	278-280°	$C_{18}H_{25}ON \cdot HBr$	dl^{\pm}	116
HO	$CH_2CH_2N(C_2H_4)_2$	base	156°	$C_{18}H_{24}ON_{2}$	- 72.5*	161
HO	CH ₂ COOH	base	265-267°	$C_{10}H_{22}O_{3}N$	68.8+	161
HO	CH ₂ CH ₂ OC ₆ H ₅	HCl	252-253°	$C_{24}H_{29}O_{2}N \cdot HCl$	57·4+	180
НО	CH ₂ CH ₂ OCH ₂ CH ₂ OH	base	b	$C_{20}H_{20}O_{3}N$	() [‡]	180
İ			270-280°	- 2029 - 5-		
HO	$CH_2CH_2CH_3$	HBr	195–196°	$C_{17}H_{27}ON \cdot HBr$	44·7‡	161
CH ₃ O	$CH_2CH_2CH_3$	HBr	278–279°	$C_{20}H_{29}ON \cdot HBr$	35.10+	161
CH ₃ COO	$CH_2CH_2CH_3$	HBr	265–267°	$C_{21}H_{29}O_2N \cdot HBr$	— 31·6 ≠	161
HO	CH_2COCH_3	HBr	248–249°	$C_{19}H_{25}O_2N \cdot HBr$	33·2 *	161
HO	CH ₂ CHOHCH ₃	HBr	210–212°	$C_{19}H_{27}O_2N \cdot HBr$	() ‡	161
HO	CH ₂ CH ₂ COOC ₂ H ₅	d-tartrate	172–173°	$C_{21}H_{29}O_{3}N \cdot C_{4}H_{6}O_{6}$	28·75‡	161
HO	CH ₂ CH ₂ COOC ₂ H ₅	salicylate	192–193°	$C_{21}H_{29}O_3N \cdot C_7H_6O_3$	()	161
HO	CH ₂ CH ₂ CH ₂ OH	base	174–175°	$C_{19}H_{27}O_2N$	— 57·22‡	161
HO	CH ₂ CH ₂ CH ₂ OH	d-tartrate	245–246°	$C_{19}H_{27}O_2N \cdot C_4H_6O_6$	()	161
НО	CH ₂ CH ₂ CH ₂ OC ₆ H ₅	<i>d</i> -camphor-sulfonate	206–207°	$C_{25}H_{31}O_2N \cdot C_{10}H_{16}O_4$	- 23·1†	180
HO	CH ₂ CH ₂ CH ₂ NHC ₆ H ₅	d-tartrate	142–143°	$C_{25}H_{32}ON_2 \cdot C_4H_6O_6$	- 31.6†	180
НО	$CH_2(CH_2)_3CH_3$	d-tartrate	165–167°	$C_{20}H_{29}ON \cdot C_4H_6O_6$	— 30·3 †	180

† Strong analgesic activity
 * Weak or no analgesic activity
 \$ see pharmacological part.

TABLE V—continued

R	R ₁	Base / Salts	m.p.	Formula	[α] _D	Ref.
	CH ₃					
НО	CH ₂ CHCH ₃	HBr	178–180°	C ₂₀ H ₂₉ ON · HBr	— 46·67†	161
НО	CH ₂ (CH ₂) ₃ CH ₃	HCI	220–221°	C ₂₁ H ₃₁ ON · HCl	56•5†	180
	CH ₃					
но	CH ₂ CHC ₂ H ₅	d-tartrate	215–217°	$\mathrm{C_{21}H_{31}ON} \cdot \mathrm{C_4H_6O_6}$	37·6 ‡	180
	CH ₃					
НО	CH ₂ CH ₂ CHC ₂ H ₅	d-tartrate	120°	$\mathrm{C_{22}H_{33}ON} \cdot \mathrm{C_4H_6O_6}$	- 32·4†	180
	CH ₃					
но	CH ₂ CH ₂ CHCH ₃	HCI	171–172°	$C_{21}H_{31}ON \cdot HCl$	— 41·83†	180
	CH ₃					
CH ₃ O	CH ₂ CH ₂ CHCH ₃	d-tartrate	168–170°	$\mathrm{C_{22}H_{33}ON} \cdot \mathrm{C_4H_6O_6}$	28·4‡	180
НО	CH ₂ (CH ₂) ₄ CH ₃	HCI	225°	C ₂₂ H ₂₃ ON · HCl	()†	180
	CH ₃					
CH ₃ O	CH ₂ CH ₂ CHC ₂ H ₅	d-tartrate	175–177°	$\mathrm{C_{23}H_{35}ON} \cdot \mathrm{C_4H_6O_6}$	— 27·1†	180
	C ₂ H ₅					
CH₃O	CH ₂ CH ₂ CHC ₂ H ₅	d-tartrate	165–167°	$\mathrm{C_{24}H_{37}ON} \cdot \mathrm{C_4H_6O_6}$	31.9#	180
	C ₂ H ₅					
но	CH ₂ CH ₂ CHC ₂ H ₅	d-tartrate	131°	$C_{23}H_{35}ON \cdot C_4H_6O_6$	34·7†	180



† Strong analgesic activity

see pharmacological part. * Weak or no analgesic activity



R	R ₁	Base / Salts	m.p.	Formula	[α] _D	Ref.
НО	$ \begin{array}{c} Br \\ \\ CH_2 - C = CH_2 \end{array} $	HBr	252–253°	C ₁₉ H ₂₄ ONBr ⋅ HBr	45•9*	161
НО	CH_{3} \downarrow $CH_{2}C=CH_{2}$ CH	base	154°	C ₂₀ H ₂₇ ON	()	161
ΉO	CH_3 CH_2 — C = CH_2	HBr	249–250°	C ₂₀ H ₂₇ ON · HBr	45·5 ‡	161
НО	$CH_2CH = CHCH_3$	base	193–195°	$C_{20}H_{27}ON$	()	161
НО	CH ₂ CH=CHCH ₃ CH ₃	HBr	148°	$C_{20}H_{27}ON \cdot HBr$	()*	161
НО	CH ₂ CH=CCH ₃ CH ₃	base	202–204°	C ₂₁ H ₂₉ ON	— 27·3†	180
НО	CH ₂ CH=CCH ₃	HBr	140°	$C_{21}H_{29}ON \cdot HBr$	61·25*	180
CH₃O	CH_{3} $ $ $CH_{2}CH=C-CH_{3}$ CH_{4}	d-tartrate	161°	$C_{22}H_{31}ON \cdot C_4H_6O_6$	43·2‡	180
COO N	CH ₂ CH=C-CH ₃	d-tartrate	203–204°	$C_{27}H_{32}O_2N_2 \cdot C_4H_6O_6$	54·7†	180

TABLE VI—continued

TABLE VI—continued

R	R ₁	Base / Salts	m.p.	Formula	[¤] _D	Ref.
	CH ₂ OCH ₃					
НО	CH ₂ CH=CCH ₃	base	162–163°	$C_{22}H_{31}O_2N$	- 93·2 *	180
	C ₂ H ₅					
НО	$CH_2CH=C-C_2H_5$	base	170–171°	C ₂₃ H ₃₃ ON	()*	180
110	C_2H_5	LID-	107 1000	C II ON IIP-		190
но	$CH_2CH = C-C_2H_5$ CH_3	пы	107-100	C ₂₃ H ₃₃ ON · HBI	()	100
НО	CH ₂ CH=CC ₂ H ₅	d-tartrate	170–172°	$C_{22}H_{31}ON \cdot C_4H_6O_6$	44·9†	180
	CH ₃					
но	$CH_2CH = C - C_2H_5$	HBr	128–129°	$C_{22}H_{31}ON \cdot HBr$	61·8†	180
	C≡CH					
НО	CH_2 $CH=C$ CH_3	d-tartrate	119–120°	$\mathrm{C_{22}H_{27}ON}\cdot\mathrm{C_4H_6O_6}$	- 21·5†	180
НО	$\begin{pmatrix} -N-CH_2CH=CH-CH_2-N-\\ \end{pmatrix}$	HCI	280–281°	$\mathrm{C_{36}H_{46}O_2N_2} \cdot \mathrm{HCl}$	— 92 ‡	180
НО	CH ₂ CH=CH-	base	192°	C ₂₅ H ₂₉ ON	()	178
НО	CH ₂ CH=CH	HBr	194–196°	C₂₅H₂9ON · HBr	67·7‡	178

TABLE VI—continued

R	R ₁	Base / Salts	m.p.	Formula	[α] _D	Ref.
HO HO HO CH_3O CH_3O CH_3COO CH_3COO CH_3CH_2COO C_6H_5COO	$CH_2 - C = CH$	base HBr <i>d</i> -tartrate base salicylate base <i>d</i> -tartrate <i>d</i> -tartrate	198-200° 160-161° 184° 103-105° 161-162° b _{0.02} 170° 103° 105-106°	$\begin{array}{c} C_{19}H_{23}ON\\ C_{19}H_{23}ON \cdot HBr\\ C_{19}H_{23}ON \cdot C_4H_6O_6\\ C_{20}H_{25}ON\\ C_{20}H_{25}ON \cdot C_7H_6O_3\\ C_{21}H_{25}O_2N\\ C_{22}H_{27}O_2N \cdot C_4H_6O_6\\ C_{26}H_{27}O_2N \cdot C_4H_6O_6\\ \end{array}$	$()- 63.0^{\ddagger}- 45.7- 95.27^{\ddagger}()- 84.3^{\ddagger}- 32.2^{\ddagger}- 34.4^{\ddagger}$	161 161 161 161 161 161 161 161
НО	$\begin{pmatrix} -N-CH_2-C\equiv C-CH_2-N-\\ \end{pmatrix}$	HCI	260–263°	$\mathrm{C_{36}H_{44}O_2N_2}\cdot\mathrm{HCl}$	4·8‡	180
НО	CH ₂ C≡C	base	175–176°	C ₂₅ H ₂₇ ON	- 116.65	178
но	CH2-C=C-	salicylate	218–219°	$C_{25}H_{27}ON \cdot C_7H_6O_3$	()*	178



R	R ₁	Base / Salts	m.p.	Formula	[¤] _D	Ref.
НО	CH2-	HBr	261–262°	$C_{23}H_{27}ON \cdot HBr$	dl‡	128
НО	CH2-	base	170–171°	C ₂₃ H ₂₇ ON	92·2	161
НО	CH2-	HBr	273–276°	$C_{23}H_{27}ON \cdot HBr$	68·15 *	180
Н	CH ₂ CH ₂	HBr	274–275°	$C_{24}H_{29}N \cdot HBr$	dl‡	178
НО	CH ₂ CH ₂	HBr	262–264°	C₂₄H₂9ON · HBr	dl†	178
НО	CH ₂ CH ₂	base	243–245°	C ₂₄ H ₂₉ ON	()	178
НО	CH ₂ CH ₂	HBr	300–301°	C₂₄H₂9ON · HBr	— 63·12†	178
НО	CH ₂ CH ₂	d-tartrate	125–126°	$\mathrm{C}_{24}\mathrm{H}_{29}\mathrm{ON}\cdot\mathrm{C}_{4}\mathrm{H}_{6}\mathrm{O}_{6}$	42·75†	178
НО	CH ₂ CH ₂	phosphate	190–192°			178
НО	CH ₂ CH ₂	camphor- sulfonate	218–220°			178

† Strong analgesic activity
 * Weak or no analgesic activity
 } see pharmacological part.

TABLE VII—continued

R	R ₁	Base / Salts	m.p.	Formula	[¤]D	Ref.
НО	CH ₂ CH ₂	bromo- methylate	239–240°	C ₂₅ H ₃₂ ONBr	42·81 ‡	178
CH ₃ O	CH ₂ CH ₂	d-tartrate	104 - 105°	$\mathrm{C_{25}H_{31}ON}\cdot\mathrm{C_4H_6O_6}$	37·4†	178
CH ₃ COO	CH ₂ CH ₂	нсі	186–187°	$C_{26}H_{31}O_2N \cdot HCl$	— 55·2†	178
НО	CH ₂ CH ₂ -	HBr	300–301°	$C_{24}H_{29}ON \cdot HBr$	+ 63·2+	178
CH ₃ O	CH ₂ CH ₂	d-tartrate	119–122°	$\mathrm{C_{25}H_{31}ON}\cdot\mathrm{C_4H_6O_6}$	+62.7+	178
НО	CH ₂ CH ₂ -	нсі	263–265°	C ₂₄ H ₃₃ ON · HCl	59·2†	178
НО	CH ₂ CH ₂ -	base	209–211°	C ₂₄ H ₃₃ ON	()	178
НО	CH ₂ CH ₂ -	base	195–196°	C ₂₄ H ₃₅ ON	()	178
НО	CH ₂ CH ₂ -	HCI	235–236°	$C_{24}H_{35}ON \cdot HCl$	57•3=	178
Н	CH ₂ CH ₂ -NO ₂	нсі	230–231°	$\mathrm{C_{24}H_{28}O_2N_2}\cdot\mathrm{HCl}$	dI†	178
НО	CH ₂ CH ₂ -NO ₂	HCI	247°	$C_{24}H_{28}O_2N_2 \cdot HCl$	84·6†	178
Н	CH ₂ CH ₂	нсі	300°	$C_{24}H_{30}N_2$	dl†	178

R	R ₁	Base / Salts	m.p.	Formula	[¤]D	Ref.
НО	CH2CH2-NH2	base	196–199°	$\mathrm{C_{24}H_{30}ON_2}$	+ 107·6≠	178
НО	CH ₂ CH ₂	base	198–199°	$C_{24}H_{30}ON_2$	107·6‡	178
НО	CH ₂ CH ₂ ——N(CH ₃) ₂	base	135–137°	$\mathrm{C_{26}H_{34}ON_2}$	89†	178
НО	CH ₂ CH ₂	base	194°	C ₂₄ H ₃₀ ON ₂	84·8†	178
НО	CH ₂ CH ₂	HCI	287–289°	$C_{24}H_{30}ON_2 \cdot HCl$	60 ·4†	178
НО	CH2CH2-OH	HCI	187–190°	$C_{24}H_{29}O_2N \cdot HCl$	70•6†	178
НО	CH2CH2-OH	base	251–252°	C ₂₄ H ₂₉ O ₂ N	()	178
НО	CH ₂ CH ₂ -OCH ₃	base	156–158°	$C_{25}H_{31}O_2N$	()	178
НО	CH ₂ CH ₂ -OCH ₃	d-tartrate	145–146°		47·9†	178
CH₃O	CH ₂ CH ₂ -OCH ₃	HCI	217–219°	$C_{26}H_{33}O_2N \cdot HCl$	— 70·7 †	178

TABLE VII—continued

R	R ₁	Base / Salts	m.p.	Formula	[α] _D	Ref.
НО	OCH ₃ CH ₂ CH ₂	base	189–190°	C ₂₅ H ₃₁ O ₂ N	()	178
НО	CH ₂ CH ₂	HCI	168–170°	$C_{25}H_{31}O_2N \cdot HCl$	69·1†	178
ĤО	CH ₂ CH ₂ -OCH ₃	нсі	238–240°	$C_{25}H_{35}O_2N \cdot HCl$	— 59·7†	178
НО	CH ₂ CH ₂ —CH ₃	HCI	284–290°	$C_{25}H_{31}ON \cdot HCl$	75·4†	178
НО	CH ₂ CH ₂ —CH ₃	base	173–174°	C ₂₅ H ₃₁ ON	()	178
НО	CH ₂ CH ₂ —SCH ₃	base	163°	C ₂₅ H ₃₁ ONS	— 106†	180
НО	CH2CH2-OCH3	base	192–194°	$C_{26}H_{33}O_3N$	()	178
НО	OCH ₃ CH ₂ CH ₂ -OCH ₃ OCH ₃	HCI	238–240°	C₂6H₃₃O₃N · HCl	— 68·1 ≠	178

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IAB	LE VII-continuea

R	R ₁	Base / Salts	m.p.	Formula	[¤] _D	Ref.
CH ₃ O	CH ₂ CH ₂ —OCH ₃ OCH ₃	base	103°	C ₂₇ H ₃₅ O ₃ N	85•7	178
НО	CH ₂ CH ₂ -OCH ₃ CH ₃	НСІ	249–251°	$C_{26}H_{33}O_2N \cdot HCl$	— 66·2†	178
НО	CH ₂ CH ₂ O	HCI	290–292°	$C_{25}H_{29}O_3N \cdot HCl$	75·53†	178
НО	CH ₂ CH ₂ -O	base	176–178°	C ₂₅ H ₂₉ O ₃ N	(—)	178
НО	CH ₂ CH ₂ -O	HCI	290–292°	C₂₅H₂9O₃N · HCl	+75·3≠	178
CH ₃ O	CH ₂ CH ₂ O	d-tartrate	171–172°	$C_{26}H_{31}O_3 \cdot C_4H_6O_6$	46•2	178

TABLE VII—continued

R	R ₁	Base / Salts	m.p.	Formula	[¤]D	Ref.
НО	OCH ₃ CH ₂ CH ₂ -OCH ₃ OCH ₃	base	181–183°	C ₂₇ H ₃₅ O ₄ N	()	178
НО	CH ₂ CH ₂ -OCH ₃ OCH ₃	нсі	240–242°	C ₂₇ H ₃₅ O4N · HCl	61·5*	178
н	CH ₂ CO-	HBr	230–231°	$C_{24}H_{27}ON \cdot HBr$	dl†	180
н	CH ₂ CO	base	173–175°	C ₂₄ H ₂₇ O ₂ N	()	178
НО	CH ₂ CO	HCI	278–279°	C ₂₄ H ₂₇ ON · HCl	— 71·91†	178
НО	CH ₂ CH(OH)	HCI	244–245°	$C_{24}H_{29}O_2N \cdot HCl$	— 70 ∙6†	180
НО	CH ₂ CO-OCH ₃	HCI	275–280°		81·5†	178
НО	CH ₂ CH(OH)-OCH ₃	HCI	234–235°	$C_{25}H_{31}O_3N \cdot HCl$	86†	178
НО	CH ₂ CO-SCH ₃	HCI	212–213°	$C_{15}H_{29}O_2NS \cdot HCl$	— 108·7†	178

TABLE VII—continued

R	R1	Base / Salts	m.p.	Formula	[α] _D	Ref.
НО	CH ₂ COO	base	214–216°	C ₂₅ H ₂₇ O ₄ N	()	178
НО	CH ₂ CO-O	HBr	250–251°	$C_{25}H_{27}O_4N \cdot HBr$	77·8†	178
CH3O	CH ₂ CO-O	d-tartrate	188–189°	$C_{26}H_{29}O_4N \cdot C_4H_6O_6$	— 57·8†	178
	NO ₂					
НО	CH ₂ CO-OCH ₃	HCI	202°	$C_{25}H_{28}O_5N_2 \cdot HCl$	74·8‡	178
НО	CH ₂ CH C ₂ H ₅	d-tartrate	140–143°	$\mathrm{C_{26}H_{33}ON}\cdot\mathrm{C_4H_6O_6}$	40•9+	180
НО	CH ₂ CH ₂ CH ₂ -	base	140–142°	C ₂₅ H ₃₁ ON	()	178
НО	CH2CH2CH2	HBr	132°	$C_{25}H_{31}ON \cdot HBr$	43+	178
НО	CH ₂ CH ₂ CO	d-tartrate	128–130°	$\mathrm{C_{25}H_{29}O_6N\cdot C_4H_6O_6}$	35•5#	180

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R	R ₁	Base / Salts	m.p.	Formula	[¤]b	Ref.
НО	CH ₂ (CH ₂) ₂ CH ₂	base	144–146°	C ₂₆ H ₃₃ ON	()	178
НО	CH ₂ (CH ₂) ₂ CH ₂	d-tartrate	179–180°	$\mathrm{C_{26}H_{33}ON} \cdot \mathrm{C_4H_6O_6}$	— 33†	178
НО	CH ₂ (CH ₂) ₃ CH ₂	base	171–173°	C ₂₇ H ₃₅ ON	57•4	180
НО	CH ₂ (CH ₂) ₃ CH ₂	HCI	278–280°	$C_{27}H_{35}ON \cdot HCl$	(—)‡	178
НО	CH ₂ CH ₂	HCI	285–287°	C ₃₀ H ₃₃ ON · HCl	85·8 <i>‡</i>	180

TABLE VII—continued

 † Strong analgesic activity
 [‡] Weak or no analgesic activity see pharmacological part.



R	R ₁	Base / Salts	m.p.	Formula	[α] _D	Ref.
НО	CH ₂ CH ₂ -N	HBr	191–193°	$C_{23}H_{28}ON_2 \cdot HBr$	+ 51•94	179
НО	CH ₂ CH ₂ —N	d-tartrate	146–147°	$\mathrm{C_{23}H_{28}ON_2}\cdot\mathrm{C_4H_6O_6}$	38·4	179
НО	CH ₂ CH ₂ -	base	207–209°	$\mathrm{C_{23}H_{28}ON_2}$	()	179
НО	CH ₂ CH ₂ -	H ₂ SO ₄	175–177°	$C_{23}H_{28}ON_2 \cdot H_2SO_4$	58•0	179
НО	CH2CH2-NH	H ₂ SO ₄	168–170°	$\mathrm{C_{23}H_{34}ON_2 \cdot H_2SO_4}$	41·2	179
НО	CH ₂ CH ₂	H ₂ SO ₄	170–175°	$\mathrm{C_{24}H_{36}ON_2 \cdot H_2SO_4}$	()	179
НО	CH ₂ CH ₂ NO	base	211–213°	$C_{22}H_{32}O_2N_2$	()	178

TABLE VIII—continued

R	R ₁	Base / Salts	m.p.	Formula	[α] _D	Ref.
НО	CH ₂ CH ₂ N O	salicylate	248–249°	$C_{22}H_{32}O_2N_2 \cdot C_7H_6O_3$	54·3	178
НО	CH ₂ CH ₂	base	221–222°	C ₂₂ H ₂₇ O ₂ N	()	180
НО	CH ₂ CH ₂	HCI	155–156°	$C_{22}H_{27}O_2N \cdot HCl$	64·6	180
НО	CH ₂ CH ₂ -0	HCI	155–156°	$C_{22}H_{27}O_2N \cdot HCl$	+ 63.8	180
CH ₃ O	CH ₂ CH ₂	d-tartrate	91–92°	$\mathrm{C_{23}H_{29}O_2N}\cdot\mathrm{C_4H_6O_6}$	— 33·3	180
CH ₃ O	CH ₂ CH ₂ -O	d-tartrate	110–112°	$\mathrm{C_{23}H_{29}O_2N}\cdot\mathrm{C_4H_6O_6}$	+ 56•4	180
НО	CH ₂ CH ₂	base	244–245°	C ₂₂ H ₂₇ ONS	()	180
НО	CH ₂ CH ₂	HCI	171–173°	C ₂₂ H ₂₇ ONS · HCl	65•5	180
НО	CH ₂ CH ₂	HCI	171–173°	C ₂₂ H ₂₇ ONS · HCl	+ 66•9	180

R	R ₁	Base / Salts	m.p.	Formula	[α] _D	Ref.
CH ₃ O	CH ₂ CH ₂ -S	d-camphor- sulfonate	188°	$C_{23}H_{29}ONS \cdot C_{10}H_{16}O_4S$	+58.2	180
COO N	CH ₂ CH ₂	d-tartrate	118–119°	$C_{28}H_{30}O_2N_2S\cdot C_4H_6O_6$	41·8	180

TABLE VIII—continued



R	R1	Base / Salts	m.p.	Formula	[¤]D	Ref.
H H H H HO HO HO HO HO HO HO HO HO HO HO	H H H H H H H H H H H H H C N C N C N C	base HCl H ₂ SO ₄ picrate HBr HBr base HCl HBr base HCl	$\begin{array}{c} b_{0\cdot05}115^{\circ}\\ 229^{\circ}\\ 195^{\circ}\\ 207^{\circ}\\ 239-241^{\circ}\\ 276-278^{\circ}\\ 260-262^{\circ}\\ 320^{\circ}\\ 222-224^{\circ}\\ 278-280^{\circ}\\ 320^{\circ}\\ 104^{\circ}\\ 216-219^{\circ}\\ 109-110^{\circ}\\ 109^{\circ}\\ 109^{$	$\begin{array}{c} C_{16}H_{21}N \\ C_{16}H_{21}N \cdot HCl \\ C_{16}H_{21}N \cdot H_2SO_4 \\ C_{16}H_{21}N \cdot C_6H_3O_7 \\ C_{16}H_{21}N \cdot HBr \\ C_{16}H_{21}ON \cdot HBr \\ C_{16}H_{21}ON \cdot HBr \\ C_{16}H_{21}ON \cdot HCl \\ C_{16}H_{21}ON \cdot HBr \\ C_{16}H_{21}ON \cdot HBr \\ C_{16}H_{21}ON \cdot HBr \\ C_{16}H_{21}ON \cdot HCl \\ C_{17}H_{20}ON \\ C_{17}H_{20}ON_2 \\ C_{19}H_{22}O_2N_2 \\ C_{19}H_{22}O_2N_2 \\ C_{19}H_{20}ON \\ C_{10}H_{20}ON \\ C_{$	$\begin{array}{c} dl \\ dl \\ dl \\ dl \\ dl \\ dl \\ -41.5 \\ (-) \\ (-) \\ +41.8 \\ (+) \\ dl \\ (-) \\ (-) \\ dl \\ (-) \\ dl \\ dl \\ (-) \\ dl \\ (-) \\ dl \\ (-) \\ dl \\ dl \\ (-) \\ (-) \\ dl \\ (-) \\ dl \\ (-) \\ (-) \\ dl \\ (-) \\ (-) \\ dl \\ (-) \\ (-) \\ (-) \\ (-) \\ dl \\ (-) \\ (-$	111, 112 111, 112 111, 112 111, 112 111, 112 180 153, 161 155 180 180 111, 112 111, 112 111, 112 111, 112 111, 112 111, 112 111, 112 111, 112
HO CH ₃ O HO	COCH ₃ COCH ₃ CONH ₂ CH ₃	salicylate	138 262–263° 172° 152–153° 187–189°	$C_{18}H_{23}O_{1}N$ $C_{19}H_{25}O_{2}N$ $C_{17}H_{22}O_{2}N_{2}$ $C_{17}H_{25}ON \cdot C_{7}H_{6}O_{3}$	197·5 187·8 dl dl	180 180 180 180

9. Synthesis of morphinan-like compounds

Many attempts have been made to modify the morphinan molecule. The opening of ring C was especially rewarding and led to a series of compounds of the benzomorphan structure (184) for which morphine-like effects were found. This class of compounds has been studied intensively by MAY, EDDY *et al.* Their work will be discussed in the second part of this volume.



In further attempts, (a) the size of a single ring, (b) the point of attachment of the iminoethane bridge or (c) the position of the nitrogen atom in the morphinan molecule were modified.

C-nor- and C-homo-N-Methylmorphinans

SUGASAWA and SAITO^(181,182) synthesized cyclopentenyl- and cycloheptenylethylamine according to the method of SCHNIDER and HELLERBACH⁽¹²⁸⁾. From these amines they obtained 3-hydroxy-*N*-methyl-*C*-normorphinan (187) and 3-hydroxy-*N*-methyl-*C*-homomorphinan (190) by HENECKA's⁽¹³²⁾ method.



In a similar way, PROTIVA *et al.*⁽¹⁸³⁾ tried without success to synthesize the analgesically inactive *C*-norderivative (187). The *C*-homoderivative (190) which on the other hand is analgesically active has also been synthesized by HENECKA and WIRTH⁽¹³³⁾.

1,3,4,9,10,10a-Hexahydro-9, 4a-(2H)-iminoethanophenanthrene (195)

The synthesis of a homoderivative (195) with a seven-membered hetero ring D was carried out by NEWMAN and MAGERLEIN⁽¹⁸⁴⁾, independently of the work on morphinans, as shown below.



1,2,3,9,10,10a-Hexahydro-6-hydroxy-11-methyl-1,4a-(4H)-iminoethanophenanthrene (202, R=OH)

Starting from the substituted 2-(2-dimethylaminoethyl)-2-phenyl-cyclohexanone (196) MAY and MURPHY (185-187) prepared the above compound (202) as shown on the flowsheet:





The substance (202, R=OH) showed only weak analgesic activity.

Compounds of the morphinan type in which the position of the nitrogen atom is modified are designated, as proposed by SUGIMOTO^(188,189), as "azades-*N*-morphinans".



des-N-morphinan

A few syntheses of such compounds are outlined below:

N-Methyl-15-aza-des-N-morphinan (208, R=H) (N-methyl-4b,9-iminoethano-4b, 5, 6, 7, 8, 8a, 9, 10-octahydrophenanthrene) was prepared by OCHIAI and HARASAWA⁽¹⁹⁰⁾ according to the following reaction scheme.



In the same way HARASAWA⁽¹⁹¹⁾ was able to prepare 3-hydroxy- (208, R=OH) and 2,3-dimethoxy-*N*-methyl-15-aza-des-*N*-morphinan. He also achieved the resolution of *N*-methyl-15-aza-des-*N*-morphinan and of the 3-hydroxy derivative (208). None of these compounds showed any analgesic activity.

3-Hydroxy-N-methyl-16-aza-des-N-morphinan (214) (N-methyl-4b,9-methanoiminomethano-4b,5,6,7,8,8a,9,10-octahydrophenanthrene) and the corresponding desoxy compound described by SUGIMOTO and OHSHIRO^(189,192) also show no analgesic activity.



In addition to these 15- and 16-aza isomers of *N*-methyl-morphinan other compounds have been synthesized in which the nitrogen atom is present in the C ring. SUGIMOTO *et al.*⁽¹⁹³⁾ obtained *N*-methyl-6-aza-des-*N*-morphinan (2-methyl-5,10b-trimethylene-1,2,3,4,4a,5,6,10b-octahydrobenzo[h]isoquino-line) and SUGIMOTO and OHSHIRO⁽¹⁹⁴⁾ its 3-hydroxy derivative (220) by the following route.



No analgesic effect was found, though compound (220) possesses weak antitussive properties⁽¹⁹⁵⁾.

In connection with the correlations between pharmacological activity and chemical structure, the synthesis of 3-hydroxy-N-methyl-7-aza-des-N-mor-

phinan (225) (9-hydroxy-3-methyl-5,10b-trimethylene-1,2,3,4,4a,5,6,10b-oc-tahydrobenzo[f]isoquinoline) was of particular interest. In this compound the distances between the functional groups ($-N-CH_3$ and HO--) and the

quaternary C-atom are the same as in 3-hydroxy-*N*-methylmorphinan (60). SUGIMOTO and KUGITA^(196,197) prepared this compound in the following Way.



The product (225), however, showed only weak analgesic activity⁽¹⁹⁸⁾.

A further isomer, *N*-methyl-8-aza-des-N-morphinan (233, R=H) (4-methyl-5,10b-trimethylene-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline) was synthesized by SUGIMOTO *et al.*⁽¹⁹⁹⁾ by the following route:



OHSHIRO⁽²⁰⁰⁾ showed that the compound (233, R = H) prepared as shown above has the same steric structure as morphine (B/C cis, C/D trans). Similarly OHSHIRO⁽²⁰¹⁾ prepared 3-hydroxy-N-methyl-8-aza-des-N-morphinan (233,
R=OH) which has an analgesic activity of the order of magnitude of codeine and also exhibits an antitussive effect.

Up to now the highest analgesic activity among these morphinan analogues was found in 3-hydroxy-9-aza-des-N-morphinan (237) (6-hydroxy-4a,10-trimethylene-1,2,3,4,4a,9,10,10a-octahydrophenanthridine) which was synthesized by SUGIMOTO and KUGITA^(202,203) as shown below.



The hydroxy derivative has an analgesic activity of the same order of magnitude as morphine, but with a considerably higher toxicity.



Compounds in which the points of attachment of the hetero ring, its size and the position of the nitrogen atom in the morphinan skeleton are modified, have been synthesized by KUGITA⁽²⁰⁴⁾.

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3-Hydroxy-N-methyl-4b,8a-ethanoiminomethano-4b, 5,6,7,8,8a,9,10-octahydrophenanthrene (245) has no analgesic activity; nor was any analgesic activity found in 3-hydroxy-N-methyl-4b,8a-methanoiminomethano-4b,5,6,7,-8,8a,9,10-octahydrophenanthrene (251), also synthesized by KUGITA⁽²⁰⁵⁾.



CHAPTER II

Pharmacology of Morphinans

1. TOXICITY AND ANALGESIC ACTION OF MORPHINANS

(a) Introduction

Side by side with the chemical work on the new synthetic analgesics their pharmacological evaluation was also carried out. The ever present stimulus to the recurring search for new synthetic analgesics has been the hope that new active compounds might be found free of the undesirable side effects of morphine itself. A further element in this continued search has been the untiring efforts of several research groups, particularly those of EDDY and SCHAU-MANN. The results of their research, contained in many publications, establishing the relationship between chemical constitution and pharmacodynamic action gave new impetus to synthetic work directed towards new analgesics. We are also indebted to them for a number of comprehensive reports and two excellent monogaphs on Opium alkaloids, especially on morphinelike synthetic compounds⁽²⁰⁷⁻²⁰⁸⁾, in which the complete literature on this subject has been collected.

As morphine is always taken as the standard preparation in investigations of new analgesics a few of the pharmacodynamic properties of this natural product may be recalled here. Its outstanding action on the central nervous system is that of raising the pain threshold. This action of therapeutic doses in man (10-20 mg s.c.) is accompanied by a sedative and euphoric action. With increasing dosage a state of somnolence approaching narcosis is reached which with a further increase in the dose can develop into deep coma.

A further effect of morphine is the depression of the respiratory centre which can appear even with therapeutic doses; breathing is slowed down and deepened, finally with reduction of the minute volume. A depression of the cough reflex parallels the analgesic action and respiratory paralysis.

With continued use of morphine the sensitivity of the organism to this substance diminishes. First there develops habituation which necessitates a continual increase of the dosage to maintain the full analgesic effect. This tolerance can lead to the most dreaded side effect of morphine, namely, addiction. This has really been the main stimulus for research in the field of synthetic analgesics. To eliminate this side effect was the main objective of

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work on the modification of the natural product and the later total syntheses of new analgesics.

The withdrawal of morphine from addicts leads to abstinence phenomena which are manifested in both physical and mental changes. The resulting symptoms can only be relieved by giving morphine or morphine-like analgesics.

A similar symptom complex can also be produced to some extent in animals. Among others, SEEVERS⁽²⁰⁹⁻²¹²⁾ and co-workers, using monkeys, EDDY⁽²¹³⁾, PIERCE and PLANT⁽²¹⁴⁾ and others using morphine-addicted dogs and rats^(215,216) could observe symptoms of abstinence or habituation.

Apart from the tests on monkeys, pharmacological experiments are unreliable and inadequate for judging on the socialogically important problem of addiction produced by analgesics⁽²¹⁷⁾. For this reason, this test for addiction-producing properties is carried out in man using the so-called "Lexington Test" as developed by ISBELL and his colleagues in Lexington^(218,21Ba,12). It is based on the fact that the abstinence symptoms brought in morphine addicts^(9,219) by withdrawal of morphine can be abolished by giving another habit-forming analgesics. This systematic examination of the addictionproducing properties of derivatives of the opiates and of new synthetic analgesics is only carried out in Lexington. Based on their findings, the World Health Organisation takes its decisions as to which new preparations have to be placed under narcotic control.

(b) Methods of testing⁽²²⁰⁾

Analgesia

All compounds contained in the following table were tested in mice and a number of them also in rats and rabbits. The tests in the mouse was partly carried out by the "hot-plate" method⁽²²¹⁾. Using this method the ED_{50} values by subcutaneous and oral administration were calculated for all active compounds with the help of "probit analysis". In another section of the tests on mice, the method of heat-stimulation of the mouse tail⁽²²²⁾ was used. By subcutaneous administration and using groups of 10 animals per dose, the mean prolongation of the reaction time by 50 per cent was measured (MED₅₀).

With rats the reaction to irradiation of the shaved skin of the back was used (223-226). For each subcutaneous dose groups of 5 animals were used and the dose necessary for an average increase in the reaction time by 50 per cent estimated.

With rabbits electric stimulation of the tooth pulp was used $^{(227-228)}$, the analgesic being given intravenously to groups of at least 3 animals. The dose necessary to increase the threshold voltage for stimulation by 50 per cent is termed the MED₅₀.

Toxicity

The lethal doses in mice (LD_{50}) were determined by subcutaneous and oral routes by Dr. Eddy in Bethesda, Maryland, USA, and by the intravenous route in the Medical Research Department of Hoffmann-La Roche, Basle, Switzerland. Values were calculated by the probit method.

(c) Results

The pharmacological properties of the analgesically active morphinans can perhaps best be illustrated by the example of Levorphanol. The differences in the action between the individual compounds are mostly of a quantitative character.

Levorphanol [(-)-3-Hydroxy-N-methyl-morphinan]

Analgesic action

In both animal^(127,229,230) and clinical^(231,232) experiments it can be shown with the help of the WOLFF-HARDY-GOODELL method that only the laevorotatory optical isomer of 3-hydroxy-N-methyl-morphinan (levorphanol) (133) possesses analgesic action whereas the *dextro*-rotatory isomer (dextrorphan) possesses none. The intensity of the effect of equal doses depends only very slightly on the mode of administration.

In contrast to morphine which exerts its analgesic action orally only in relatively high doses, levorphanol is active in man, both orally and parenterally, in doses of the order of 1-2 mg.

Comparative tests showed that 2 mg of levorphanol were equal in analgesic activity to (233-235):

10 mg	morphine
50 (75) mg	pethidine (Dolantin ^(R))
10 mg	oxycodone (Eukodal ^(R))
7•5 mg	ketobemidone (Cliradon ^(R)) and
2 mg	dihydromorphinone (Dilaudid ^(R)).

Duration of analgesic action

In clinical tests the activity of the rapeutic doses of Levorphanol (2 mg/kg) lasted for $4^{(236)}$ to $15^{(237)}$ hr.

Toxicity

The general action of 3-hydroxy-N-methyl-morphinan is – as is true for morphine – fundamentally different from one animal species to another. Accordingly the cause of death can vary from one species to another: respiratory paralysis or generalized convulsions.

Species Route	Morphine HCl mg/kg	rac. 3-Hydroxy- <i>N</i> - methyl-morphinan hydrobromide mg/kg	()-3-Hydroxy-N- methyl-morphinan tartrate mg/kg	(+)-3-Hydroxy-N- methyl-morphinan tartrate mg/kg
Mouse i.v.	225	33	45	75
Rat s.c.	300	108	135	500
Rabbit i.v.	135	18·5	22-5	22·5

The lethal doses found by FROMHERZ⁽²⁹²⁾ are as follows:

Respiratory Depression. Even with the apeutic doses of Levorphanol there is a slight depression of respiration which, under certain circumstances, can even be made use of the rapeutically⁽²³⁵⁾. With higher doses (5-10 mg) the respiratory depression increases⁽²³⁸⁾.

Habituation. Prolonged administration of Levorphanol brings about a slight habituation which necessitates an increase of the doses^(239,240).

Addiction. Although abstinence symptoms can scarcely be observed even after its administration for several months^(241,235), Levorphanol does possess addictive properties as could be shown by ISBELL in the "Lexington-Test"^(242,243).

The other side effects of Levorphanol are also similar to those of morphine as described by EDDY, HALBACH and BRAENDEN⁽²⁴⁴⁾. The side-effects of the morphinans are generally weaker than those of morphine even though the analgesic effects are stronger.

The analgesic action of morphinans

The following tables lists the toxicity and analgesic action of a representative selection of morphinans. The preparations were investigated mainly in the form of their water-soluble salts but the values given are calculated in terms of the bases. Many of these figures are unpublished. Other fuller details can, in some cases, be found in the given original literature. In general it can be said that various investigators, using different methods, have, on the whole, found similar results for the same compounds. Even when using different animal species the activities were not fundamentally different.

N-Methyl-morphinans

Compounds with the nitrogen atom unsubstituted $(R_1=H)$ are inactive. While compounds without substitution at the 3-position (R=H) are active the degree and length of activity are generally increased by introduction of a hydroxy group (R=OH). Displacement of the hydroxy group to the 2- or 4-position brings about loss of activity. The introduction of further substituents in the 1- or 2-positions reduces the activity. Methylation of the hydroxy group in the 3-position $(R=OCH_3)$ causes some reduction of activity while with higher alkyl or alkenyl groups $(R=OC_2H_5, OC_3H_7, OCH_2--CH=CH_2$ etc.) the compounds are inactive. Acylation of the hydroxy at position 3 scarcely alters the intensity of the analgesic action, but its duration is shortened. Morphinans are generally as active when given orally as when given parenterally. It has been found for all morphinans so far investigated that after resolution into their optical isomers only the laevorotatory isomers, corresponding to the natural product morphine, are active while the antipodes are inactive.

(-)-3-Hydroxy-*N*-methyl-morphinan (Dromoran^(R), Levorphanol) selected on the grounds of its favourable toxicity and activity data in animal experiments has proved of clinical value.

N-Alkyl-morphinans

An increase in the number of carbons in the N-alkyl group (e.g. $R_1=C_2H_5$, n— C_3H_7) leads first to preparations with reduced analgesic action while a further lengthening of the chain (R= C_4H_9 , C_5H_{11} , C_6H_{13}) again produces more active compounds. Branching of the chain does not bring about any definite change. The introduction of O- or N-functions into the alkyl chain R_1 leads invariably to a reduction or loss of analgesic activity.

N-Alkenyl- and N-alkynyl-morphinans

The short, straight-chain N-alkenyl and N-alkynyl morphinans ($R_1 = -CH_2$ --CH==CH₂ or CH₂--C==CH) show no analgesic action. They possess, on the contrary, an antagonistic activity (see section 2). This property is confined to representatives of the (-)-series.

Compounds with longer alkenyl chains only show this action to a small extent while an analgesic action is again evident (e.g. $R_1 = -CH_2 - CH_2 - CH_3 = C(CH_3)_2$. The introduction of *O*- and *N*-functions leads to a loss of both activities.

N-Aralkyl-morphinans

This class of compounds includes representatives with very high activity displayed by members with two or three carbon atoms between the nitrogen of the ring system and the aryl group. *N*-Benzyl derivatives as well as morphinans with longer aralkyl groups are inactive. The introduction of an *O*-function next to the aryl ring scarcely affects the activity (e.g. $R_1 = -CH_2COC_6H_5$). Substitution of the aralkyl group by the corresponding cyclo-alkyl group (e.g. $R_1 = -CH_2CH_2C_6H_{11}$) leads to loss of analgesic activity. Of the changes in analgesic activity caused by substitution in the aryl ring, an increase is only observed with nitro- or amino groups in the *p*-position.

TABLE X. MORPHIN, CODEIN,



	R	R ₁	Salt / Base
I E I E I E I E E E I I	Morphin Codein H HO HO CH ₃ COO CH ₂ =CH—CH ₂ O CH ₂ =CH—CH ₂ O CH ₂ =CH—CH ₂ O CH ₃ CH ₂ CH ₂ O HO	CH ₃ CH ₃ CH ₃ CH ₃ CH ₃ CH ₃ CH ₃ CH ₃ CH ₃ H	HCl H ₃ PO ₄ H ₃ PO ₄ HBr tartrate tartrate tartrate HBr HBr HBr HBr HBr
(±)	HO-	CH ₃	HCI
(±)	HO-U	СН3	HCI
(+)	CH ₃ O	CH ₃	HBr
()	CH2==CHCH2 HO	CH3	citrate
()		CH3	tartrate

N-METHYL-MORPHINANS

	DL ₅₀ 1	Mouse	ED ₅₀	MED ₅₀	MED ₅₀	MED ₅₀	MED ₅₀
	s.c.	i.v.	$(1 \times SE limits)$ Mouse s.c.	Mouse s.c.	Rat s.c.	Rabbit i.v.	$(1 \times SE limits)$ Mouse orally
	mg	/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg
	370	225		10	5	2.5	ca. 25
	200	70		25	75	10	45
		20.8		13.7	20.0	3.0	
		33.0	0.7	1.7		1.0	
		33.0	0.48	0.95	1.07	0.5	2.0
	>300	42.3	44.3	50	60.5		
		32.0		1.0			
		32.5		30	5		
		19.7		8.5			
		26.9		>10			
		45.0		130			
		38•4		>30			
		29•2		8-0			
I		50		>50			
		28		10–12			
		28		2.0			

TABLE XI. N-ALKYL-MORPHINANS



	R	R ₁	Salt/Base
	HO HO HO HO HO HO	CH ₂ CH ₃ CH ₂ CH ₃ CH ₃ CH ₂ (CH ₂) ₂ CH ₃ CH ₂ (CH ₂) ₃ CH ₃ CH ₂ (CH ₂) ₄ CH ₃ CH ₂ CH(CH ₃) ₂ CH ₂ -CH(CC ₄) ₂ CH ₂ CH ₂ CH(C ₂ H ₅) ₂ CH ₃	HBr HBr tartrate HCl HCl HBr tartrate
()	НО	CH ₂ CH ₂ CHC ₂ H ₅ CH ₃	tartrate
()	НО	CH ₂ CHC ₂ H ₅	tartrate
(—) (—)	CH₃O CH₃O	$CH_2CH_2CH(CH_3)_2$ CH_2CH_2CH(C_2H_5)_2	tartrate tartrate
()	CH₃O	$-CH_2CH_2CHC_2H_5$	tartrate
	HO HO HO HO HO HO HO HO	$\begin{array}{l}CH_{2}CH_{2}CH(CH_{3})_{2} \\CH_{2}CH_{2}-N(C_{2}H_{5})_{2} \\CH_{2}CH_{2}COOC_{2}H_{5} \\CH_{2}CH_{2}CH_{2}OH \\CH_{2}CH_{2}OCH_{2}CH_{2}OH \\COCH_{3} \\COCH_{3} \\COCH_{3} \\CH_{2}CH_{2}CH_{2}NHC_{6}H_{5} \\CH_{2}CH_{2}CH_{2}CC_{6}H_{5} \end{array}$	HCI HCI tartrate HCI HCI tartrate camphor- sulfonate
()	НО	CH ₂ COCH ₃	Sanonato

(except *N*-methyl)

 DL ₅₀	50 Mouse ED ₅₀		MED ₅₀	MED ₅₀	MED ₅₀	MED ₅₀
s.c.	i.v.	$(1 \times SE minus)$ Mouse s.c.	Mouse s.c.	Rat s.c.	Rabbit i.v.	$(1 \times SE \text{ limits})$ Mouse orally
mg	g/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg
 	}					
187	27.0	9.5	15.4	20.0	3.85	19.8
I.	38		inactive			
	26.7	1.12	4.9			32.8
	26.9	0.36	0.30		1	12.3
	26.2	0.53	0.67			17•6
	48.0		5.0			
	40.3	2.60	4.8			
	13.1	1.28	1.4			24.8
	35	8.39	>50			75.1
	13·7 28	8.96	21 inactive			
	20		mactive			
	27.0	5.2	10			Į
	42.5	0.50	1.28			14-2
	39.0	0.50	inactive	ł		Ì
	72		>25	1		
	50		> 25	{		[
	62.8		inactive			
	>1000 n.o.		inactive			
	2000 p.0.		inactive	1		
	>1000 p.o.		inactive			
	357 p.o.		4			
	40	1	5			
	55-2		inactive		inactive	

TABLE XII. N-ALKENYL- AND



	R	R ₁	Salt/Base
(_) (_) (_)	HO HO CH ₃ O (CH ₃) ₂ NCOO	$CH_2CH=CH_2$ $CH_2CH=CH_2$ $CH_2CH=CH_2$ $CH_2-CH=CH_2$	HBr tartrate HBr HBr
()	но 0=РО но	CH ₂ CH=-CH ₂ CH ₃	base
	НО НО СН₃О НО СН₃О НО	$-CH_{2}-C=CH_{2}$ $-CH_{2}-CH=CH-CH_{3}$ $-CH_{2}-C\equiv CH$ $-CH_{2}-C\equiv CH$ $-CH_{2}-C\equiv CH$ $-CH_{2}-C=CH=C(CH_{3})_{2}$ $-CH_{2}-CH=C(CH_{3})_{2}$ $-CH_{2}-CH=C(C_{2}H_{3})_{2}$	HBr HBr tartrate HBr base tartrate HBr
(—)	НО	$-CH_2$ $-CH_3$ $-CH_2$ $-CH_3$ $-CH_$	tartrate
()	НО	$CH_2CH=C(C_2H_5)_2$	HBr
()	COO N	-CH ₂ CH ₃ -CH ₂ CH=C CH ₃	tartrate
()	НО	$-CH_{2}CH = C - C = CH$	tartrate
()	НО	CH ₂ OCH ₃ CH ₂ CH=C	HCl
()	но	$-N-CH_2CH=CH-CH_2-N-$	НСІ
()	НО	NCH ₂ C≡CCH ₂ N	HCI

N-ALKYNYL-MORPHINANS

DL ₅₀ N	Aouse	ED ₅₀	MED ₅₀	MED ₅₀	MED ₅₀	MED ₅₀
s.c.	i.v.	$(1 \times SE limits)$ Mouse s.c.	Mouse s.c.	Rat s.c.	Rabbit i.v.	$(1 \times SE limits)$ Mouse orally
mg/	kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg
	40·5 26 24·4 71		30 inactive inactive >30			
	150		ca. 50			
	30·7 50·7 48·3 110 29 20 28·4	1·5 2·87 2·12	inactive 9.5 >30 inactive 2.1 inactive 7.3 3.0			55-0 inactive 28-6
	28.4	2.87	7•3			60.1
	40		3-5			
	31.6	3.09	6.8			63.7
	35	11-2	24.0			inactiv
	70		inactive			
	35		inactive			
		ł				

TABLE XIII.



	R	R ₁	Salt/Base
()	НО	CH2-	HBr
()	но	CH ₂ CH ₂	HCl
(±)	н	CH ₂ CH ₂	HBr
()	НО	CH ₂ CH ₂	HBr
(+)	НО	CH ₂ CH ₂	HBr
()	CH₃O	CH ₂ CH ₂	tartrate
(+)	CH₃O	CH ₂ CH ₂	tartrate
()	CH ₃ COO	CH ₂ CH ₂ -	HCI
()	но	CH ₂ CH ₂ -	HCl
()	НО	CH ₂ CO	HCl
()	НО	CH ₂ CH	HCl
		о́н	
(+)	Н	CH ₂ CO-	HBr
()	НО	CH ₂ CH ₂ O-	HCI
()	но	CH ₂ CH ₂ CH ₂ -	HBr
(—),	но	CH ₂ CH ₂ CO	tartrate
()	НО	CH ₂ (CH ₂) ₂ CH ₂	tartrate

N-Aralkyl-morphinans

DL ₅₀	Mouse	ED ₅₀	MED ₅₀	MED ₅₀	MED ₅₀	MED ₅₀
s.c.	i.v.	Mouse s.c.	Mouse s.c.	Rat s.c.	Rabbit i.v.	Mouse orally
mg	;/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg
 400	800	100	50	40.3		
750	31.7	2•36	45	8.6	1.8	
600	28.3	38•7	28.0	50.0		
500	32•4	0.113	0.12	0.16	0.02	1.22
600	129.5	100	inactive	inactive		
388	16.5	0.69	1.0	1.6	0.26	
	240	100	inactive	inactive		
615	20.6	0.09	0.14	0.2	0.04	
400	31.7	0•49	0.68		0.20	7.12
400	18-2	0.094	0.091	0.18	0.044	4•4
204	2.7	0.145	0.136	0.27	0•064	4.0
600	114	100	inactive	inactive		
ca. 400	31.9	10.3	27•4	100.0	3.5	:
>400	58.8	20.8	38.6	50•0		inactive
	20		11			
>400	358 p.o.	3.57	5•4		2.2	31-2

TABLE XIII-

	R	R ₁	Salt/Base	
()	НО	CH ₂ CH-	tartrate	
()	но	C_2H_5 $CH_2(CH_2)_3CO-$	base	
()	но	CH ₂ CH ₂ -CH ₃	нсі	
(—)	но	CH ₂ CH ₂ OCH ₃	tartrate	
()	но	CH ₂ CH ₂ -OCH ₃	HCI	
()	CH₃O	CH ₂ CH ₂ -OCH ₃	HCl	
()	но	CH ₂ CH ₂ —OH	HCI	
()	но	CH ₂ CO-OCH ₃	HCl	
()	но	CH ₂ CHOH-OCH ₃	HCl	
		∠OCH ₃		
()	НО	CH ₂ CH ₂	HCI	
()	НО	CH ₂ CH ₂ -OCH ₃	HCI	
		CH ₃		
()	НО	CH ₂ CH ₂ -NH ₂	base	
(+)	но	CH ₂ CH ₂ -NH ₂	base	
(±)	НО	CH ₂ CH ₂ -NH ₂	HCl	
()	но	CH ₂ CH ₂ -	base	
		NH2		
()	НО	CH ₂ CH ₂	HCl	
		NH ₂		i i

continued

 DL ₅₀	Mouse	ED ₅₀	MED ₅₀	MED ₅₀	MED ₅₀	MED ₅₀
s.c.	i.v.	$(1 \times SE limits)$ Mouse s.c.	Mouse s.c.	Rat s.c.	Rabbit i.v.	$(1 \times SE \text{ limits})$ Mouse orally
 mg	/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg
	75	14.7	35•7	50•0		53.6
>400	15.6	51.9	29.0	10-0	5.0	inactive
>750	22.7	0.09	0.27	0.3	0.02	1.64
>400	22•4	0.16	0.36	0.36	0.1	3.15
679	31.9	1.17	1.82	1.82	0.64	
>600	45.3	3.55	9•0	18-3	2.7	
613	22.7	0.16	0.45	0.91	0.14	5.54
>600	62.6	1.04	0.92	2.7	0.67	13.47
>600	31-1	0.23	0.64	0.64	0.32	8.8
>800	22.8	2.1	7•5		1.0	20.2
>800	32.0	1.00	4.2	8.2	1.83	19•3
	11·7 70p.o.	0.018	0.02	0.10	0.025	1.69
>400	20.0	100	inactive	inactive	5.0	
207	41.2	0.49	1.10	2.5	0.60	
665	40 ∙0	0.69	1.25	2.5	0.75	14.61
160	8.3	0.04	0.083	2.5	0.044	2.51

TABLE XIII-

	R	R ₁	Salt/Base
()	НО	CH ₂ CH ₂ —N(CH ₃) ₂	base
()	НО	CH ₂ CH ₂	HCI
(±)	Н	CH2CH2-NO2	HCI
()	НО	CH ₂ CH ₂ -SCH ₃	base
()	но	CH ₂ CO-SCH ₃	HCl
()	но	CH ₂ CH ₂	HCI
()	НО	CH ₂ CH ₂ -OCH ₃	HCl
()	СН₃О	OCH ₃ CH ₂ CH ₂ —OCH ₃ OCH ₃	base
()	но	CH ₂ CO-OCH ₃	HCI
()	но	CH_2CH_2 $-O$ O	HCI
(+)	но	CH ₂ CH ₂ -O	HCI
(—)	CH3O	CH ₂ CH ₂ -O	tartrate
()	НО	CH ₂ COO O	HBr

continued

 DL ₅₀	Mouse	ED ₅₀	MED ₅₀	MED ₅₀	MED ₅₀	MED ₅₀
s.c.	i.v.	(1 × SE limits) Mouse s.c.	Mouse s.c.	Rat s.c.	Rabbit i.v.	(1 × SE limits) Mouse orally
 mg	/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg
>600	40.7	0.13	0.21	0.80	0.20	1.23
400	22.7	0.034	0.14	0.27	0.046	2.37
600	425 p.o.	73·2	3.64	10.0	1.82	
600	500 p.o.	0.045	0.12	0.21	0.05	1.09
600	920p.o.	0.82	1.4	2.5	0.30	2.85
	1000 p.o.		inactive			
400	32.3	92.5	45.5	inactive		
600	25.6	100	50.0	inactive		
600	1000 p.o.	128.5	9·2		3.0	
800	22.9	0.065	0.18	0.22	0.05	3.33
400		100	100 (tox.)	100·0(tox.)		
>600	36•5	1.68	3.65	10-0	1.46	
>600	41.0	0.26	0.22	0.20	0.08	5.42

TABLE XIII-

	R	R ₁	Salt/Base
()	CH30	CH ₂ COO	tartrate
()	но	CH ₂ CH=CH-	HBr
()	но	CH₂C≡C-	base
()	НО	OCH ₃ CH ₂ CH ₂ —OCH ₃ OCH ₃	HCI

TABLE XIV.



	R	R ₁	Salt/Base
()	но	CH ₂ CH ₂ -N	tartrate
()	НО	CH ₂ CH ₂ -NH	H ₂ SO ₄
()	НО	CH ₂ CH ₂ CH ₃	H ₂ SO ₄
()	но	CH ₂ CH ₂ -	H ₂ SO ₄
()	но	CH ₂ CH ₂ -	нсі

DL ₅₀ Mouse		ED ₅₀	MED ₅₀	MED ₅₀	MED ₅₀	MED ₅₀
s.c.	i.v.	$(1 \times SE limits)$ Mouse s.c.	Mouse s.c.	Rat s.c.	Rabbit i.v.	$(1 \times SE limits)$ Mouse orally
mg	/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg
>600	25.8	10-2	3.7			
>600	55-0	>50	8-2	50	1.6	
>600	34.0	>100	inactive	inactive		
ca. 400	>5000 p.o.	>100	inactive	inactive		

N-HETEROCYCLYLALKYL-MORPHINANS

 DL50	Mouse	ED ₅₀	MED ₅₀	MED ₅₀	MED ₅₀	MED ₅₀
s.c.	i.v.	$(1 \times SE limits)$ Mouse s.c.	Mouse s.c.	Rat s.c.	Rabbit i.v.	$(1 \times SE limits)$ Mouse orally
mg	/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg
347	24.3	0.063	0.14	0.35	0.07	3.68
26	6.0	>100	inactive	inactive		
>600	13-1	>150	50.0	50	2.0	
181	15.6	0.19	0·47		0.23	12:42
2 26	25.3	0.01	0.023	0.007	0.004	0.73

TABLE XIV-

	R	R1	Salt/Base
(+)	но	CH ₂ CH ₂	HCI
(+)	СН₃О	CH ₂ CH ₂ -0	Camphor- sulfonate
()	COO N	CH ₂ CH ₂ -	tartrate
()	НО	CH ₂ CH ₂	HCI
()	НО	CH ₂ CH ₂ -NO	salicylate
()	CH₃O	CH ₂ CH ₂	tartrate

TABLE XV.



	R	R ₁	Salt/Base	
(+) (-) (+) (+) (+) (-)	CH ₃ O, 10-hydroxy CH ₃ O, 10-oxo CH ₃ O, 10-hydroxy HO HO	CH_3 CH_3 CH_3 $I6 N-CH_3$ $CH_2CH=CH_2$ $CH_2CH=CH_2$	HCl base HCl HCl bromo- allylate iodomethy-	
()	но	CH ₂ CH ₂ -	bromo- methylate	
(-)	НО	N-oxide		

continued

 DL50	Mouse	ED ₅₀	MED ₅₀	MED ₅₀	MED ₅₀	MED ₅₀
s.c.	i.v.	$(1 \times SE limits)$ Mouse s.c.	Mouse s.c.	Rat s.c.	Rabbit i. v.	$(1 \times SE limits)$ Mouse orally
 mg	/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg
	20	>100.0	inactive			
	100		inactive			
	35		0.06			
	35	0.019	0.025	0.014	0.009	
>600	650p.o.	70.1	inactive			
	40		inactive			

MISCELLANEOUS MORPHINANS

 DL ₅₀ Mouse		ED ₅₀	MED ₅₀	MED ₅₀	MED ₅₀	MED ₅₀
s.c.	i.v.	$(1 \times \text{SE limits})$ Mouse s.c.	Mouse s.c.	Rat s.c.	Rabbit i.v.	$(1 \times SE \text{ limits})$ Mouse orally
 mg	/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg
	50 50 50 71 5		50 50 50 100 10			
	14		inactive			
600	4.9	1.52	5.0		1.0	
	100		inactive			

N-Heterocyclylalkyl morphinans

Very active compounds are also found in this class. Again the hetero group must be of an aromatic nature and be joined to the nitrogen of the ring system by a two carbon chain.

Miscellaneous morphinans

The introduction of an oxygen function at position 10, quaternizing of active morphinans or the formation of their *N*-oxides lead to a loss of activity.

2. MORPHINANS WITH ANTI-MORPHINE ACTIVITY

(a) Introduction

The use of morphine and similarly acting synthetic analgesics is limited by their side effects. In addition to the already mentioned addictive properties and respiratory depression there are other undesirable symptoms such as nausea, vomiting, obstipation and impairment of diuresis etc.

As early as 1915 POHL⁽¹⁶⁰⁾ found that N-allyl-norcodcinc was capable of inhibiting the respiratory depression brought about by morphine; this was later confirmed by HART⁽²⁴⁵⁾. He could also show that N-allyl-nor-morphine possesses similar properties^(17,246). According to UNNA⁽¹⁵⁹⁾ previous administration of the antagonist may prevent respiratory depression by the analgesic.

The above work was followed by many investigations in animals and in man which widened our knowledge of the antagonistic action of N-allyl-normorphine (Nalorphine, Nalline^(R), Lethidrone^(R)) and of its useful applications.

It was obvious to search also in the morphinan series for compounds with morphine-antagonistic properties. The pharmacological investigation⁽²⁴⁷⁾ of (-)-3-hydroxy-*N*-allyl-morphinan tartrate^(153,161) (Levallorphan, Lorfan^(R)) did indeed show that this compound, which is only a weak analgesic in high doses, possesses antagonistic properties^(67,247,248) in very low doses.

This antagonism is not solely directed specifically against respiratory depression but also affects in higher doses the analgesic action of morphine, codeine⁽²⁴⁹⁾ and similar analgesics. Nevertheless, there are quantitative differences which allow the use of appropriate doses to maintain analgesia, while avoiding respiratory depression. This relationship was also found in animal experiments using other morphinans of similar structure (e.g. (-)-3-hydroxy-*N*-propargyl⁽²⁵⁰⁻²⁵²⁾, (-)-3-acetoxy-*N*-allyl-⁽²⁵⁰⁾, (-)-3-ethoxy-*N*-allyl-⁽²⁵⁰⁾ and (-)-3-hydroxy-*N*-methallyl-morphinan⁽¹⁸⁰⁾). This antagonistic action of these compounds is confined to the laevorotatory morphinan derivatives sterically related to morphine⁽²⁵³⁾, whereas (+)-3-hydroxy-*N*-allyl-morphinan has neither analgesic nor morphine-antagonistic properties.

(b) *Pharmacology*

Respiratory depression

Of the greatest practical importance is the stimulating action of morphine antagonists in respiratory depression. FROMHERZ, PELLMONT and BESEN-DORF^(67,247,248) showed that with conscious rabbits the respiratory depression caused by 15 mg/kg i.v. morphine was abolished by 0.1 mg/kg i.v. Levallorphan (Fig. 1); this was also observed by BENSON *et al.*⁽²⁵³⁾ on anaesthetized rabbits.



Fig. 1. Conscious rabbits; breathing: nasal cannula; at (1)—morphine 15 mg/kg i.v.; at (2)—Levallorphan 0.1 mg/kg i.v.

In clinical trials^(250,254-261,261a-261g) the amount of Levallorphan required to abolish respiratory depression is dependent on the dosage of the particular analgesic used. With 10 mg of morphine, 2 mg of Dromoran and 75-100 mg of Pethidinc, which are equally analgesic active at these doscs, only 0·2-0·25 mg of Levallorphan were necessary to prevent the depressive effect on respiration. According to SWERDLOW⁽²⁶²⁾ and to ZINDLER and GANZ⁽²⁶³⁾ much higher doses of the antagonist than would ever be used therapeutically were devoid of any significant undesirable side-effects.

Analgesia

As already mentioned, the morphine antagonistic action of Levallorphan also effects the analgesic action. In the rat, using the radiant heat method of ERCOLI and LEWIS⁽²²⁶⁾, Levallorphan abolished the analgesic action of a five-fold dose of Levorphanol and reduced that of a twenty-fold dose⁽²⁴⁷⁾.

Antagonism to other effects of narcotics

Other side-effects of the narcotics are also antagonized by Levallorphan and by a few closely related compounds. In experiments with dogs and on mcn, HART and BECKER showed that Levallorphan was able to abolish the stimulating effect of morphine on the intestinal tone⁽²⁶⁴⁾. SCHAUMANN⁽²⁶⁵⁾ observed that intestinal peristalsis could also be inhibited. Paralysis of the stretch reflex brought about by opium alkaloids and synthetic morphine-like analgesics was completely or at least partially abolished and the raised fluid pressure due to morphine was lowered⁽²⁶⁶⁾. Diuresis⁽²⁶⁷⁻²⁷⁰⁾, nausea and vomiting^(271,272) were equally favourably affected by Levallorphan. Central stimulation⁽²⁷²⁾ and increased motility produced by strong analgesics in certain animal species was abolished⁽²⁵³⁾. KJELLGREN⁽²⁷³⁾ showed that contraction of the sphincter of Oddi produced by morphine or pethidine^(274,275) was prevented by Levallorphan and the rise in biliary pressure reduced and shortened. The antagonism of Levallorphan is not restricted to the opium alkaloids. In animal experiments the hypotensive, the respiratory depressant and the hyper-glycaemic actions of 1-2 mg/kg Cannabis indica i.v. was unmistakably antagonized⁽²⁷⁶⁾. A competitive antagonism with Levallorphan⁽²⁷⁷⁾ is also observed against cytotoxic action.

Besides the description of this antagonistic action of Levallorphan there are to be found in the literature reports on other properties of this interesting compound. SCHULTZE-GÖRLITZ⁽²⁷⁸⁾, for example, experienced in trials on himself an action of Levallorphan resembling that of Mescaline cr lysergic acid diethyl amide; its possible use in psychotherapy is discussed by WIESER⁽²⁷⁹⁾.

Addiction

Neither (-)-3-hydroxy-N-allyl-morphinan nor its methyl ether causes addiction, nor are they metabolized in the animal to compounds with such properties. Accordingly, the narcotic antagonists are, by a decision of the World Health Organisation (WHO), not subjected to narcotic control $(^{280})$. Their antagonistic action against the main side-effect of the narcotics, addiction, is, however, not so marked as that on respiratory depression.

A certain hope for a favourable effect on addiction⁽²⁸¹⁾ is to be found in one property of the narcotic antagonists⁽²⁸²⁾ which is already used clinically⁽²⁸³⁾, i.e. for the diagnosis of addiction, as in the so-called "allyl-test"^(284,285). According to observations by EDDY, FRASER and ISBELL the administration of a subcutaneous injection of a narcotic antagonist to an addict leads within a few minutes to an acute abstinence syndrome which is very similar to that brought about by a sudden withdrawal of the narcotic⁽²⁸⁶⁾. Experiments aimed at preventing tolerance and physical dependence ever to arise have been made by combining the narcotic with its antagonist when being given to non-addicted patients⁽²⁸⁷⁾.

Mode of action

The antagonistic action of Levallorphan is thus directed against the specific properties of morphine and morphine-like analgesics while unspecific properties like convulsions⁽⁶⁷⁾ and toxicity⁽²⁴⁷⁾ are not affected. The mode of action

of the narcotic antagonists has not yet been fully elucidated. Most authors explain it as a displacement process in the central nervous system^(252,258,288) at the receptors concerned. According to SCHWAB *et al.*⁽²⁵⁷⁾ there are also indications pointing at still other mechanisms besides competitive inhibition.

Results

A large number of the N-alkenyl and alkynyl morphinans listed in Table XII pages 80-81 have been tested thoroughly for their antagonistic properties towards narcotics⁽²⁸⁹⁾. Activity was only found in a small number of the analogues of Levallorphan, as, for example, (-)-3-hydroxy-N-propargyl morphinan. Its antagonistic action is generally less than that of Levallorphan. It could for example abolish respiratory depression in rats caused by codeine but the required dose was twice as large as that of Levallorphan⁽²⁹⁰⁾. Its analgesic action is of the same order as that of Nalorphine which latter it also resembles closely in its side-effects⁽²⁹¹⁾. (-)-3-Hydroxy-N-(3,3-dimethyl-allyl)-morphinan also possesses interesting properties in that it has about the same analgesic action as morphine but also its characteristic side effects (nausea, vomiting etc.); the respiratory depressing effect, however, is less than that of morphine⁽²⁹¹⁾.

Toxicity

The general picture of morphine toxicity⁽²⁶⁷⁾ varies according to the animal species and this has also been found to be qualitatively true for Levorphanol. As Levallorphan is closely related structurally to Levorphanol it was to be expected that their toxic effects in different animal species would be

Species	Route	Levallorphan mg/kg	Levorphanol mg/kg	
Mouse	i.v.	42	50	
Mouse	s.c. 240		225	
Mouse	p.o. 350			
Rat	i.v.	40		
Rat	s.c.	870	160	
Rat	p.o.	850		
Guinea pig	s.c.	140	190	
Rabbit	i. v.	17	22	
Rabbit	s.c.	>200	ca. 200	
Rabbit	p.o.	p.o. 50		
Cat	i.v. 10		_	
	(anaesthetized)			
Cat	p.o.	50	10	
Dog	s.c.	25	-	
Dog	p. o.	50	-	

TABLE XVI

MORPHINANS

similar. Toxicological investigations by FROMHERZ⁽²⁹²⁾ confirmed this as shown in Table XVI.

In the mouse Levallorphan when injected intravenously in sublethal doses causes laboured breathing and convulsions. The typical Straub tail phenomenon, characteristic of morphine preparations, is unmistakably apparent with toxic doses only. In rats, on the other hand, the reaction is mainly one of depression as with Levorphanol; the same is true for Guinea pigs. Rabbits after toxic doses of Levallorphan collapse with opisthotonus and trismus; respiration is not slowed. With lethal subcutaneous doses the animals die after flaccid paralysis, and with intravenous doses in convulsions. Cats react to high oral doses with clonic convulsions, while dogs lie down quietly, the respiration being hardly affected.

(c) Clinical use

The following indications for the clinical use of Levallorphan are based on its properties discussed above:

- abolition of the respiratory depression caused by analgesics, also in cases of overdosage and poisoning with narcotics^(282,288,293-296)
- as a diagnostic in narcotic addiction (allyl test)⁽²⁸⁴⁻²⁸⁵⁾
- in child birth:⁽²⁹⁷⁻³⁰⁰⁾ for the abolition or reduction of the respiratory depression of the mother caused by morphine-like analgesics and also for the abolishing asphyxia of the new-born child as Levallorphan passes the placental barrier and has a similar action on the foetus.
- in anaesthesia⁽³⁰¹⁻³¹¹⁾ for the reduction and abolition of respiratory depression caused by the use of morphine-like analgesics.

In view of these properties the narcotic antagonists are used clinically in anaesthesia where protection against respiratory depression usually lasts from $1\frac{1}{2}$ to 3 hr⁽³¹²⁾.

3. ANTI-TUSSIVE ACTION OF MORPHINANS

(a) Introduction

As mentioned already only the *laevo*-rotatory isomers in the morphinan series, corresponding in their optical configuration to morphine, possess an analgesic action. *Dextro*-rotatory morphinans which are structurally related to the natural product Sinomenine have no analgesic properties; this was also established for the *dextro*-rotatory isomer of morphine prepared from Sinomenine^(313,314).

The importance of morphine is not dependent only on its use as an analgesic. Its methyl ether, codeine, present in opium only in small amounts, is prepared, like many other derivatives, from morphine and is of great importance as a cough remedy and analgesic. This compound may cause addiction though not to the same extent as morphine. BENSON, STEFKO and RANDALL⁽³¹⁵⁾ have examined racemic 3-hydroxy-*N*-methyl-morphinan (Racemorphan) and its two optical isomers (Levorphanol and Dextrorphan) for their anti-tussive properties. They did, in fact, find the desired action with Racemorphan as well as with its two optical isomers and established that in Racemorphan and Levorphanol, which are active analgesics, it was accompanied by morphine-like side effects.

Surprising, however, was the finding that the *dextro*-rotatory isomer, (+)-3-hydroxy-*N*-methyl-morphinan, although analgesically inactive, possessed anti-tussive properties and was free from the side-effects of the *laevo*-rotatory isomer. It was soon shown that in this series not only was there a separation from the analgesic effect but also from the addictive properties.

This was even more marked with (+)-3-methoxy-*N*-methyl-morphinan (Dextromethorphan) which by analogy with codeine could be expected to show an increase of the anti-tussive action over that of Dextrorphan; this was demonstrated by RANDALL *et al.*⁽³¹⁵⁾. This compound is also free from the side-effects which are still present in its analgcsic antipode [(-)-3-methoxy-*N*-methyl-morphinan, Levomethorphan] as well as in the corresponding racemate (3-methoxy-*N*-methyl-morphinan, Racemethorphan).

(b) Pharmacological study of Dextromethorphans

Of the *dextro*-rotatory morphinans (+)-3-methoxy-*N*-methyl-morphinan (Dextromethorphan), which has been introduced into therapy as a cough suppressing agent (Romilar^(R)) has obviously been most thoroughly investigated both pharmacologically and clinically. The pharmacological studies carried out by PELLMONT and BÄCHTOLD⁽³¹⁶⁾ and RANDALL, STEFKO and BENSON^(315,317,318) led to the following results:

Toxicity

Its toxicity was compared with that of codeine^(315,316), the tests being carried out in several animal species and by different routes of administration (Table XVII). The toxicity picture was mainly one of convulsions. Respiratory depression only appeared at lethal doses.

Anti-tussive activity

The effect of Dextromethorphan on the experimental cough was tested by four different methods:

Cough produced by soap powder⁽³¹⁹⁾. This method is based on the observation that when soap powder is blown into the trachea of a cat anaesthetized with Numal^(R) coughing is induced. The degree of reduction in intensity and number of coughs after administration of the preparation was determined. In this test, Dextromethorphan possessed equal efficacy with codeine⁽³¹⁶⁾.

MORPHINANS

Species	Route	DL ₅₀ Dextromethorphan mg/kg	DL ₅₀ Codeine mg/kg
Mouse	i.v. s.c. p.o.	37 275 165	80 370 250
Rat	s.c. p.o.	740 350	700
Rabbit	i.v.	19	48
Dog	i.v. s.c.	>10 >20	

TABLE XVII

Cough produced by ammonia⁽³²⁰⁾. This method is a modification of the above test in which coughing is produced by inhalation of dilute ammonia (1:4). With ammonia stimulation the threshold dose is somewhat higher than in the soap powder test, the value for Dextromethorphan being 2 mg/kg and that for codeine 3.5 mg/kg, both given intravenously. In this test Dextromethorphan is thus somewhat more active than codeine⁽³¹⁶⁾.

Cough produced by nerve stimulation. This method described by DOMEN-JOZ⁽³²¹⁾ is based on the electrical stimulation of the intact superior laryngeal nerve of the anaesthetized cat. Dextromethorphan and codeine are equally active, the effective dosage being 2 mg/kg i.v. for both⁽³¹⁶⁾.

Cough experiments with the conscious dog. Tests were carried out according to the method of STEFKO and BENSON⁽³¹⁸⁾, based on the production of coughing by electrical stimulation of conscious animals which previously had had electrodes inserted into the submucosa of the trachea. A marked inhibition of coughing was obtained with 2 mg/kg Dextromethorphan s.c.

Thus, using four different test methods and two different animal species in the conscious and anaesthetized state, when giving Dextromethorphan by intravenous and subcutaneous administration, a marked antitussive action equal in effect to that of codeine can be obtained $^{(316)}$.

Test for analgesic action

PELLMONT and BÄCHTOLD examined Dextromethorphan for analgesic action using the radiant heat method of HARDY, WOLFF and GOODELL⁽²²³⁾ and as modified by ERCOLI and LEWIS⁽²²⁶⁾. In both rats and dogs no analgesic action could be found^(315,317).

Action on the respiratory tract

With certain animals (rabbits) an increase of respiratory volume could be determined while with others (cats) there was a decrease. The bronchi were not constricted by Dextromethorphan^(315,316), and it had no effect on expectoration⁽³²²⁾. The compound had no respiratory depressing properties⁽³¹⁵⁾.

Effect on diuresis

In morphine-like compounds the inhibition of diuresis more or less parallels the analgesic action. Dextromethorphan has no effect on diuresis when tested in doses of 35 mg/kg s.c.⁽³¹⁶⁾.

Mode of action of cough inhibition caused by Dextromethorphan

PELLMONT and BÄCHTOLD⁽³¹⁶⁾ assumed that the point of attack of Dextromethorphan, as with codeine, would be a central one. At some not exactly determined spot the cough reflex path is interrupted.

The same authors have also examined Dextromethorphan for its action on circulation, on the small intestine of the rabbit, for inhibition of inflammation and for its effect on permeability.

Morphinans with anti-tussive activity

Of the many (+)-morphinans tested parmacologically for their anti-tussive properties, none possesses a singificantly stronger action than Dextromethorphan. From these experiments the following conclusions as to the relationship between chemical constitution and anti-tussive activity of the morphinans could be drawn⁽³²³⁾.

(a) With higher alkyl ethers the activity diminishes in the following order:

$$--CH_2--CH_2=CH_2 > --C_2H_5 > CH_2CH_2N(C_2H_5)$$

> --CH_2CH_2CH_3

(b) The anti-tussive activity of N-aralkyl derivatives of (+)-morphinans does not parallel the analgesic action of the corresponding (-)-isomers. The (+)-isomers of the strongly analgesic (-)N-[2-(2-furyl)-ethyl]- and N-[2-(2-thienyl)-ethyl]-3-hydroxymorphinans, which are 60 and 45 times more strongly analgesic than (-)-3-hydroxy-N-methyl morphinan, proved to be 3 to 5 times less effective as cough inhibitors than Dextromethorphan. This was equally true for their methyl ethers.

(c) Substitution at position 2 and formation of an N-oxide reduced the anti-tussive property.

MORPHINANS

(c) Clinical use

After ISBELL and FRASER^(242.324) had established that Dextromethorphan did not possess any addictive properties, CASS *et al.*⁽³²⁵⁻³²⁷⁾, CAPELLO and DI PASQUALE⁽³²⁸⁾, encouraged by the favourable results of the animal tests submitted this compound to clinical trials. These showed that 10–15 mg Dextromethorphan had the same activity as 15 mg codeine and was better tolerated ⁽³²⁹⁾, there being no symptoms of narcotic or euphoricaction^(330,331), no habituation or addiction⁽³³²⁻³³⁴⁾.

Dextromethorphan neither reduced⁽³³¹⁾ nor promoted⁽³²²⁾ expectoration.

In view of these properties Dextromethorphan is used in medicine as an addiction-free, codeine-like cough remedy. It is particularly recommended for use in paediatrics⁽³³¹⁾ in different forms of bronchitis and persistent cough^(331,335,336) in the therapy of different forms of phthisis^(332,333,337). It is also successfully applied in aerosols^(337,338).

According to GRAFE⁽³³⁹⁾ Dextromethorphan is also valuable in pleuritic puncture, pneumothorax, thoracoscopy and bronchoscopy. GUIDI and GAR-DIN⁽³⁴⁰⁾ describe its use in geriatrics.

4. ANTI-RHEUMATIC ACTION OF MORPHINANS

The alkaloid Sinomenine, isolated from the roots of *Sinomenium acutum*, a climbing plant from the forests of Southern Japan, is the only compound found in nature which belongs to the series enantiomorphic to morphine. According to the literature Sinomenine has a therapeutic action in rheumatism⁽¹⁴⁹⁾ and is used in Japanese medicine⁽³⁴¹⁾. The pharmacological properties of this compound and clinical results in the treatment of rheumatism have been described by SHIGERU TAKAORI⁽³⁴²⁾ who also discusses a possible mode of action.

The scanty indications on the use of Sinomenine in rheumatism therapy led JÜRGENS and BÄCHTOLD⁽³⁴³⁾ to test, in the egg-white⁽³⁴⁴⁾ and the SEITTER⁽³⁴⁵⁾ "rheumatism tests", (+)-3-hydroxy-*N*-methyl-morphinan (Dextrorphan) which, in the morphinan series, corresponds sterically to the natural product Sinomenine. It was shown that Dextrorphan is strongly active in both tests; for example even $\frac{1}{160}$ of the lethal dose caused a definite reduction of phenol red excretion which is about twice that obtained with 10 mg/kg of cortisone given orally.

In the clinical trials which followed, however, Dextrophan was found to be inactive in chronic arthritis. On the other hand certain favourable effects were found in degenerative arthroses, tendinoses, spondylitis and sclero- $dcrma^{(155)}$.

5. METABOLISM OF MORPHINANS

(a) Analytical methods

The interest awakened in the different morphinans was not confined to their pharmacodynamic properties but extended to their metabolism, their distribution in the living organism and to their metabolites. In order to be able to answer the questions which arose, analytical methods had first to be worked out for characterizing the compounds of the morphinan type itself and for the small amounts of metabolites isolated from biological material.

Of further interest was the analytical differentiation between, on the one hand, racemic and *laevo*-rotatory morphinans (e.g. Racemorphan, Levorphanol) whose application is subjected to the laws governing the use of narcotics and, on the other hand, the *dextro*-rotatory isomers (e.g. Dextromethorphan) which are free from this control.

To deal with these problems a whole series of analytical methods was worked out. Most of these methods were similar to those already in use for the morphine alkaloids and the morphine-like analgesics.

Of the many methods proposed a few purely physical, like the estimation of ultraviolet⁽³⁴⁶⁾ and infrared⁽³⁴⁷⁾ spectra and the X-ray methods^(348,349) are worthy of special mention. Others depend upon precipitation and crystallization procedures⁽³⁵⁰⁻³⁵⁵⁾ or consists in the colorimetric estimation of the basic compounds⁽³⁵⁶⁾.

As the therapeutic doses of (-)-3-hydroxy-*N*-methyl-morphinan tartrate (Levorphanol, Dromoran^(R)), owing to its strong analgesic action, are very small (1·5-2 mg), the amounts of administered product or of metabolites to be expected in biological material are minute and demand very sensitive methods for their detection. KAISER and JORI^(357,358) were the first to recommend paper chromatography for this purpose and developed an appropriate working technique which was soon improved by JATZKEWITZ^(359,360), CURRY and POWELL⁽³⁶¹⁾, BROSSI, HÄFLIGER and SCHNIDER⁽³⁶²⁾, VIDIC^(363,364), WAGNER⁽³⁶⁵⁾ and BONNICHSEN et al.⁽³⁶⁶⁾ by varying the developing solvent, the detecting reagents and by the use of specially pretreated papers. An interesting development in paper chromatographic analysis is described by FI-SCHER and OTTERBECK⁽³⁶⁷⁾; with it they were able to separate a mixture of 19 morphine derivatives and synthetic analgesics.

In addition to the appropriate paper chromatographic methods other ways were found for estimating very small quantities of morphinans. WILL-NER⁽³⁶⁸⁾, for example, specially recommended paper electrophoresis when the results from chromatography are doubtful. The method was particularly suited for the separation of basic compounds.

A further possibility of identification is by microscopic characterization of isolated crystalline compounds are described by BRANDSTÄTTER-KUNERT, KOFLER and KOSTENZER⁽³⁶⁹⁾.

In order to distinguish between the three forms of 3-hydroxy-N-methylmorphinan: Racemorphan, Dextrorphan, Levorphanol, CLARKE^(370.371) developed an elegant microchemical method. This was also applicable to the identification of their methyl ethers: Racemethorphan, Levomethorphan and Dextromethorphan = Romilar^(R). Using the technique of the hanging microdrop and with a special reagent for each group of morphinans, the *dextro*and *laevo*-rotatory isomers were found to give amorphous precipitates while those formed from the racemates were crystalline. With the help of this method which can be used for quantities as small as 0.2 μ g an analytical differentiation between the addictive forms of 3-hydroxy- and 3-methoxy-Nmethyl-morphinans and the *dextro*-rotatory isomers is possible.

(b) Results

With the help of these methods metabolic products, mainly of the morphinans prepared on a technical scale, were investigated analytically.

BROSSI, HÄFLIGER and SCHNIDER⁽³⁶²⁾ showed that the morphinans were excreted by the organism partly unchanged and partly with elimination of substituent groups, while leaving the morphinan skeleton intact. On administering (+)-3-methoxy-N-methyl-morphinan (Dextromethorphan) to dogs, these authors found in the urine, besides a small amount of starting material, 11-15 per cent of its metabolic products. The following three different metabolites of dextromethorphan could be identified:

- -0.8-3.7 per cent (+)-3-methoxy-morphinan formed by N-demethylation
- -1.8-4.2 per cent (+)-3-hydroxy-*N*-methyl-morphinan formed by splitting off of the methoxy group, and finally
- -1.7-3.0 per cent (+)-3-hydroxy-morphinan formed by simultaneous splitting off the ether and by N-demethylation.

On the other hand it is remarkable that these authors could not identify similar decomposition products after administration of (-)-3-hydroxy-*N*-methyl-morphinan (Levorphanol) and (-)-3-hydroxy-*N*-allyl-morphinan (Levallorphan).

WOODS, MELLET and ANDERSEN⁽³⁷²⁾ shortly afterwards showed by using N-C¹⁴-methyl-labelled levorphanol, that this compound was also demethylated in the body, proof of this being the formation of C¹⁴O₂ as a result of biological breakdown; this agrees with the results of similar experiments using morphine^(373,374). According to ADLER *et al.*⁽³⁷⁵⁻³⁷⁸⁾ codeine is also broken down partly to an *N*-demethylated and partly to an *O*-demethylated compound (morphine) but is also excreted as free or bound codeine. Similar results were observed with pethidine: it was found by PLOTNIKOFF *et al.*⁽³⁷⁹⁻³⁸¹⁾ and BURNS *et al.*⁽³⁸²⁾ to be demethylated at the nitrogen atom.

The biological breakdown of the morphinans is not confined to the *N*-methyl compounds. MANNERING and SCHANKER^(383,384) who studied the metabolism of (-)-3-hydroxy-*N*-allyl-morphinan (Levallorphan, Lorfan^(R))

identified (-)-3-hydroxy-morphinan, indicating partial deallylation. In experiments with rats they obtained, in quantities greater than the *N*-deallylated compound, a substance of unknown structure containing an additional oxygen atom. A comparison with the oxidation product of morphine⁽³⁸⁵⁾ and with the oxidation and photo-oxidation products of (+)-3-methoxy-*N*-methyl morphinan⁽²⁰⁶⁾, both of which have been oxidized in the 10-position, led to the conclusion that the new oxygen atom was attached at another than at 10 position⁽³⁸³⁾. The same authors isolated from the urine of rabbits a further metabolite of unknown structure.

In order to clear up the kinetics of enzymatic O- and N-demethylation of morphinans and morphine derivatives TAKEMORI and MANNERING⁽³⁸⁶⁾ examined the liver microsomes of mice treated with these compounds and have drawn attention to certain connections between chemical constitution and the demethylation reaction.

The demethylation found in the living organism could also be reproduced in vitro. AXELROD^(387,388) showed that the liver is the only organ whose microsomal fraction is capable of carrying out an *N*-demethylation of narcotics. His results were shortly afterwards confirmed and extended by several research workers, among them MANNERING *et al.*^(389,390) and HERKEN *et al.*⁽³⁹¹⁾.

References

- 1. R. GREWE, Naturwissenschaften 33, 333 (1946).
- 2. R. GREWE, Angew. Chem. 59, 198 (footnote) (1947).
- 3. J.A. BARLTROP, J. Chem. Soc. 399 (1947).
- 4. J. M. GULLAND and R. ROBINSON, Mem. Manchester Phil. Soc. 69, 79 (1925).
- 5. C.SCHÖPF, Ann. Chem. 452, 211 (1927).
- 6. C.I. WRIGHT and F.A. BARBOUR, J. Pharmacol. Exp. Therap. 53, 34 (1935).
- 7. L.F. SMALL, N.B. EDDY, E. MOSETTIG and N. HIMMELSBACH, U.S. Publ. Hith. Rep. No. 138 (1938).
- 8. N.B.EDDY, Ann. N.Y. Acad. Sci. 51, 51 (1948).
- 9. C.K. HIMMELSBACH, J. Pharmacol. Exp. Therap. 67, 239 (1939).
- 10. L.E.LEE, J. Pharmacol. Exp. Therap. 75, 161 (1942).
- 11. G. STORK and L. BAUER, J. Amer. Chem. Soc. 75, 4373 (1953).
- 12. N.B.Eddy, H.HALBACH and O.J.BRAENDEN, Bull. World Health Organ. 17, 569 (1957).
- 13. O.J.BRAENDEN, N.B.EDDY and H.HALBACH, Bull. World Health Organ. 13, 937 (1955).
- 14. E.FOURNEAU, Chimie et Industrie 39, 1043 (1938).
- 15. A.L. MORRISON and H. RINDERKNECHT, Festschrift E. C. Barell, 253 (1946).
- 16. F.BERGEL and A.L.MORRISON, Quart. Revs. (London) 2, 349 (1948).
- 17. E.L. MCCAWLEY, E.R. HART and D.F. MARSH, J. Amer. Chem. Soc. 63, 314 (1941).
- 18. A.H. BECKETT, J. Pharm. Pharmacol. 4, 425 (1952).
- Meperidin, Demerol, Isonipecain, Pantalgin, Amphosedal, Dolantin, Dolantal, Dolosal, Dispadol, Mefedina, Adolan, Dolvanol, Centralgin, Sauteralgyl, Antiduol, Piridosal, Algil, Dolopethin, Spasmedal, Spasmodolin, Suppolosal.
- 20. P.A.J.JANSSEN, Synthetic Analgesics, Part I, Diphenylpropylamines, Pergamon Press (1960).
- 21. J. CASSADAY and M. T. BOGERT, J. Amer. Chem. Soc. 61, 2461, 3055 (1938).
- 22. N.B. EDDY, J. Pharmacol. Exp. Therap. 48, 183 (1933).
- 23. N.B.EDDY, J. Pharmacol. Exp. Therap. 51, 75 (1934).
- 24. N.B.EDDY, J. Pharmacol. Exp. Therap. 52, 275 (1934).
- 25. N.B. EDDY, J. Pharmacol. Exp. Therap. 55, 354, 419 (1935).
- 26. D. GINSBURG and R. PAPPO, J. Chem. Soc. 1524 (1953).
- 27. A.LOEFFLER and D.GINSBURG, J. Amer. Chem. Soc. 76, 3731 (1954).
- 28. B.BELLEAU, J. Amer. Chem. Soc. 75, 1159 (1953).
- 29. W.BORSCHE and B.SCHACKE, Ber. Deutsch. Chem. Ges. 56, 2498 (1923).
- 30. N.B.EDDY, J. Pharmacol. Exp. Therap. 58, 159 (1936).
- 31. W.H. KIRKPATRICK and P.T. PARKER, J. Amer. Chem. Soc. 57, 1123 (1935).
- 32. E. MOSETTIG and R. A. ROBINSON, J. Amer. Chem. Soc. 57, 902 (1935).
- 33. E. MOSETTIG and E. MEITZNER, J. Amer. Chem. Soc. 56, 2738 (1934).
- 34. F. WINTERNITZ, N.J.ANTIA, M. TUMLIROVA and P. LACHAZETTE, Bull. soc. chim. France, 1817 (1956).
- 35. J.LEE, A.ZIERING, S.D.HEINEMAN and L.BERGER, Festschrift E.C. Barell, 264 (1946).
- 36. J. LEE, A. ZIERING, S. D. HEINEMAN and L. BERGER, J. Org. Chem. 12, 885 (1947).
- 37. R. M. ANKER, A. H. COOK and I. M. HEILBRON, J. Chem. Soc. 917 (1945).
- 38. F.BERGEL, J.W.HAWORTH, A.L.MORRISSON and H.RINDERKNECHT, J. Chem. Soc., 261 (1944).
- 39. J.A. BARLTROP, J. Chem. Soc., 958 (1946).
- 40. C.F. KOELSCH, J. Amer. Chem. Soc. 67, 569 (1945).
- 41. A.D. MACDONALD, G. WOOLFE, L. BERGEL, A.L. MORRISSON and H.RINDERKNECHT, Brit. J. Pharmacol. 1, 4 (1946).
- 42. L.H.GOODSON, C.J.W.WIEGAND and J.S.SPLITTER, J. Amer. Chem. Soc. 68, 2174 (1946).
- 43. R. B. MOFFET and W. M. HOEHN, J. Amer. Chem. Soc. 69, 1792 (1947).
- 44. E. C. DOODS, W. LAWSON, S. A. SIMPSON and P. C. WILLIAMS, J. Physiol. (London) 104, 47 (1945).
- 45. U.S. Pat. 2506588.
- 46. U.S. Pat. 2276618; 2276619.
- 47. Brit. Pat. 512560; 513512.
- 48. U.S. Pat. 2223373.
- 49. D.R. Pat. 185733.
- 50. R.Ss.LIWSCHITZ, M.Ss.BAINOWA, G.I.BASILEWSKAJA, E.I.GENKIN, N.A.PREOBRA-ZENSKI, J.M.ROSANOWA and S.A.BARANOWA, *Chem. Zentr.* 2, 7974 (1952).
- 51. U.S. Pat. 2369611; 2352020.
- 52. G.STORK and H. CONROY, J. Amer. Chem. Soc. 73, 4748 (1951).
- 53. M.D.SOFFER, R.A.STEWART, J.C.CAVAGNOL, H.E.GELLERSON and E.A.BOWLER, J. Amer. Chem. Soc. 72, 3704 (1950).
- 54. ST. GOLDSCHMIDT and W.L.C. VEER, Rec. trav. chim. 67, 489 (1948).
- 55. E.L. MAY and J.G. MURPHY, J. Org. Chem. 20, 1197 (1955).
- 56. F. WINTERNITZ and R.M. THAKKAR, Bull. soc. chim. France, 471 (1952).
- 57. V. BOECKELHEIDE, J. Amer. Chem. Soc. 69, 790 (1947).
- 58. V. BOECKELHEIDE and W. M. SCHILLING, J. Amer. Chem. Soc. 72, 712 (1950).
- 59. J. H. BURCKHALTER and S. H. JOHNSON JR., J. Amer. Chem. Soc. 73, 4832 (1951).
- 60. J. H. BURCKHALTER and S. H. JOHNSON JR., J. Amer. Chem. Soc. 73, 4827 (1951).
- 61. H. KASPARECK and K. PFROEPFER, Arzneimittel-Forsch. 8, 673 (1958).
- 62. O. EISLEB and O. SCHAUMANN, Deutsch. Med. Wchschr. 65, 967 (1939).
- 63. O.EISLEB, Ber. Dcutsch. Chem. Ges. B 74, 1433 (1941).
- 64. K. FROMHERZ, Arch. Exp. Pathol. u. Pharmakol. 173, 86 (1933).
- 65. O.SCHAUMANN, Arch. Exp. Pathol. u. Pharmakol. 196, 109 (1940).
- 66. N.B.EDDY, H. HALBACH and O.J. BRAENDEN, Bull. World Health Organ. 17, 772 (1957).
- 67. K. FROMHERZ and P. PELLMONT, Arch. Exp. Pathol. u. Pharmakol. 218, 136 (1953).
- 68. P.J. COSTA and D.D. BONNYCASTLE, J. Pharmacol. Exp. Therap. 113, 310 (1955).
- 69. O. SCHAUMANN, Arch. Exp. Pathol. u. Pharmakol. 216, 48 (1952).
- 70. D.R.Pat. 752755.
- 71. Brit.Pat. 591992; 609763.
- 72. A.ZIERING and J.LEE, J. Org. Chem. 12, 911 (1947).
- 73. U.S. Pat. 2498433.
- 74. I. N. NAZAROV, N.S. PROSTAKOV and N.I. SHVETSOV, J. Gen. Chem. USSR 26, 3117 (1956).
- 75. I. N. NAZAROV, A. SH. SHARIFKANOV, J. Gen. Chem. USSR 27, 2063 (1957).
- J. WEIJLARD, P.D. ORAHOVATS, A.P. SULLIVAN, G. PURDUE, F.K. HEATH and K. PFIS-TER, J. Amer. Chem. Soc. 78, 2342 (1956).
- 77. F.BERGEL, N.C.HINDLEY, A.L. MORRISSON and H.RINDERKNECHT, J. Chem. Soc. 269 (1944).
- 78. J. DIAMOND, W. F. BRUCE and F. T. TYSON, J. Org. Chem. 22, 399 (1957).
- 79. J.W.KISSEL, J.R.ALBERT and G.C.BOXILL, J. Pharmacol. Exp. Therap. 134, 332 (1961).
- P.A.J.JANSSEN, C.J.E. NIEMEGEERS and K.H.SCHELLEKENS, Arzneimittel-Forsch. 10, 955 (1960).
- 81. R. E. LISTER, Brit. J. Pharmacol. 15, 254 (1960).

- 82. Chem. Eng. News 38, 42 (1960).
- 83. L.F. FIFSER and E.B. HERSHBERG, J. Amer. Chem. Soc. 57, 2192 (1935).
- 84. L.F. FIESER and H.L. HOLMES, J. Amer. Chem. Soc. 58, 2319 (1936).
- 85. L. F. FIESER and H. L. HOLMES, J. Amer. Chem. Soc. 60, 2548 (1938).
- 86. E. SPEYER and K. KOULEN, Ann. Chem. 438, 34 (1924).
- 87. R.S. CAHN, J. Chem. Soc. 702 (1930).
- 88. H.L.HOLMES and K.M.MANN, J. Amer. Chem. Soc. 69, 2000 (1947).
- 89. R. GHOSH and R. ROBINSON, J. Chem. Soc. 506 (1944).
- 90. J.C. BARDHAN and S.C. SENGUPTA, J. Chem. Soc. 2520 (1932).
- 91. M.T.BOGERT, Science 289 (1933).
- 92. D. PERLMAN, D. DAVIDSON and M. T. BOGERT, J. Org. Chem. 1, 288 (1937).
- 93. R. GREWE, Ber. Deutsch. Chem. Ges. B. 72, 426 (1939).
- 94. R. GREWE, Ber. Deutsch. Chem. Ges. B. 72, 785 (1939).
- 95. R. GREWE, Ber. Deutsch. Chem. Ges. B. 76, 1072 (1943).
- 96. D. C. HIBBIT and R. P. LINSTEAD, J. Chem. Soc. 470 (1936).
- 97. F. TIEMANN, Ber. Deutsch. Chem. Ges. B. 33, 3710 (1900).
- 98. R. GREWE, Ber. Deutsch. Chem. Ges. B. 76, 1076 (1943).
- 99. R. ROBINSON and S. SUGASAWA, J. Chem. Soc. 3163, 3173 (1931).
- 100. Z. KITASATO and R. ROBINSON, J. Chem. Soc. 785 (1932).
- 101. R.ROBINSON and S. SUGASAWA, J. Chem. Soc. 789 (1932).
- 102. R. ROBINSON and S. SUGASAWA, J. Chem. Soc. 280 (1933).
- 103. R. ROBINSON, The Structural Relations of Natural Products, Clarendon Press (1955).
- 104. C. SCHÖPF and K. THIERFELDER, Ann. Chem. 497, 22 (1932).
- 105. C. SCHÖPF, H. PERREY and I. JÄCKH, Ann. Chem. 497, 59 (1932).
- 106. C. SCHÖPF and K. THIERFELDER, Ann. Chem. 537, 143 (1939).
- 107. C. SCHÖPF, Naturwissenschaften 39, 241 (1952).
- 108. A.R. BATTERSBY and R.BINKS, Proc. Chem. Soc. 360 (1960).
- 109. A.R. BATTERSBY and B.J.T. HARPER, J. Chem. Soc. 3526 (1962).
- 110. A.R. BATTERSBY, R. BINKS and B.J.T. HARPER, J. Chem. Soc. 3534 (1962).
- 111. R. GREWE and A. MONDON, Ber. Deutsch. Chem. Ges. B. 81, 279 (1948).
- 112. R. GREWE, Angew. Chem. 59, 194 (1947).
- 113. C.F. KOELSCH and N.F. ALBERTSON, J. Amer. Chem. Soc. 75, 2095 (1953).
- 114. O. SCHNIDER, Swiss Pat. 253710.
- 115. E. SCHLITTLER and R. MERIAN, Helv. Chim. Acta 30, 1339 (1947).
- 116. O.SCHNIDER and A.GRÜSSNER, Helv. Chim. Acta 32, 821 (1949).
- 117. O.SCHNIDER, Swiss Pat. 252755.
- 118. M.S. NEWMAN and A.S. SMITH, J. Org. Chem. 13, 592 (1948).
- 119. M.G. VAN CAMPEN, D.F. MEISNER and S.M. PARMERTER, J. Amer. Chem. Soc. 70, 2296 (1948).
- 120. O. SCHNIDER and J. HELLERBACH (unpublished).
- 121. R. GREWE, A. MONDON and E. NOLTE, Ann. Chem. 564, 161 (1949).
- 122. E. OCHIAI and M. IKEHARA, Pharm. Bull. (Tokyo) 2, 72 (1954).
- 123. E. OCHIAI and M. IKEHARA, Pharm. Bull. (Tokyo) 2, 109 (1954).
- 124. E. OCHIAI and M. IKEHARA, Pharm. Bull. (Tokyo) 3, 291 (1955).
- 125. W.W. SAWTELLE and L. L. ZAGER, Fed. Proc. 8, 297 (1949).
- 126. L.L.ZAGER, W.W.SAWTELLE, E.B.GROSS, S.F.NAGYFY and R.T.TIDRICK, J. Lab. Clin. Med. 34, 1530 (1949).
- 127. L.O.RANDALL and G.LEHMANN, J. Pharmacol. Exp. Therap. 99, 163 (1950).
- 128. O. SCHNIDER and J. HELLERBACH, Helv. Chim. Acta 33, 1437 (1950).
- 129. A. BISCHLER and B. NAPIERARLSKI, Ber. Deutsch. Chem. Ges. B. 26, 1903 (1893).
- 130. W.H. WHALEY and T.R. GOVINDACHARI, "The preparation of 3,4-dihydroisoquinolines and related compounds by the Bischler-Napieralski Reaction", Organic Reactions Vol.VI, 74, Wiley, New York (1951).

- 131. R.GREWE, R.HAMANN, G.JACOBSEN, E. NOLTE and K. RIECKE, Ann. Chem. 581, 85 (1953).
- 132. H. HENECKA, Ann. Chem. 583, 110 (1953).
- 133. H.HENECKA and W.WIRTH, Medizin und Chemie (Verlag Chemie GmbH, "Bayer" Leverkusen) 5, 321 (1956).
- 134. M. SASAMOTO, Pharm. Bull. (Tokyo) 8, 324, 329, 980 (1960).
- 135. S. SUGASAWA and R. TACHIKAWA, Tetrahedron 4, 205 (1958).
- 136. J. HELLERBACH, Swiss Pat. 280674.
- 137. O. SCHNIDER and J. HELLERBACH, Helv. Chim. Acta 34, 2218 (1951).
- 138. E. E. P. HAMILTON and R. ROBINSON, J. Chem. Soc. 1029 (1916).
- 139. W. M. WHALEY and T. R. GOVINDACHARI, "The Pictet-Spengler Synthesis of Tetrahydroisoquinolines and related compounds", *Organic Reactions* 6, 151, Wiley, New York (1951).
- 140. S. SUGASAWA and R. TACHIKAWA, J. Org. Chem. 24, 2043 (1959).
- 141. R.GREWE, H.POLLMANN and M.SCHNOOR, Ber. Deutsch. Chem. Ges. B. 84, 527 (1951).
- 142. R.A.BENKESER, C.ARNOLD, R.F.LAMBERT and O.H.THOMAS, J. Amer. Chem. Soc. 77, 6042 (1955).
- 143. D. GINSBURG and R. PAPPO, J. Chem. Soc. 938 (1951).
- 144. D. ELAD and D. GINSBURG, J. Amer. Chem. Soc. 76, 312 (1954).
- 145. D. ELAD and D. GINSBURG, J. Chem. Soc. 3052 (1954).
- 146. M. GATES and G. TSCHUDI, J. Amer. Chem. Soc. 74, 1109 (1952).
- 147. M.GATES and G.TSCHUDI, J. Amer. Chem. Soc. 78, 1380 (1956).
- 148. J. A. BARLTROP and J. E. SAXTON, J. Chem. Soc. 1038 (1952).
- 149. H. KONDO and E. OCHIAI, Ann. Chem. 470, 224 (1929).
- 150. K. Goto and T. ARAI, Ann. Chem. 547, 194 (1941).
- 151. K. GOTO, I. YAMAMOTO and S. MATSUMOTO, Bull. Agr. Chem. Soc. Japan. 19, 1 (1955).
- 152. K. GOTO, H.YAMASAKI and I.YAMAMOTO, Proc. Japan Acad. 34, 60 (1958).
- 153. O. SCHNIDER and A. GRÜSSNER, Helv. Chim. Acta 34, 2211 (1951).
- 154. O.SCHNIDER, A.BROSSI and K.VOGLER, Helv. Chim. Acta 37, 710 (1954).
- 155. A. BÖNI, Z. Rheumaforsch. 12, 23 (1953).
- 156. A. BROSSI and O. SCHNIDER, Helv. Chim. Acta 39, 1376 (1955).
- 157. C.W.DEN HOLLANDER, U.S. Pat. 2819272; 2915479.
- 158. N.C. HINDLEY, Brit. Pat. 832025.
- 159. K. UNNA, J. Pharmacol. Exp. Therap. 79, 27 (1943).
- 160. J. POHL, Z. exp. Pathol. and Therap. 18, 370 (1915).
- 161. J. HELLERBACH, A. GRÜSSNER and O. SCHNIDER, Helv. Chim. Acta 39, 429 (1956).
- 162. A.H.BECKETT, Angew. Chem. 72, 686 (1960).
- 163. A.H.BECKETT, "Stereochemical Factors in Biological Activity" in E.JUCKER Fortschritte der Arzneimittelforschung, Birkhäuser-Verlag, Basel, 1, 455 (1959).
- 164. H. CORRODI, J. HELLERBACH, A. ZÜST, E. HARDEGGER and O. SCHNIDER, Helv. Chim. Acta 42, 212 (1959).
- 165. J. KALVODA, P. BUCHSCHACHER and O. JEGER, Helv. Chim. Acta 38, 1847 (1955).
- 166. D.ARIGONI, J. KALVODA, H. HEUSSER, O. JEGER and L. RUZICKA, Helv. Chim. Acta 38, 1857 (1955).
- 167. G.STORK, J. Amer. Chem. Soc. 74, 768 (1952).
- 168. G. STORK in R.H.F. Manske and H.L. Holmes "The Alkaloids", *Chemistry and Physiology* 2, 171, Academic Press, New York (1952).
- 169. H. RAPOPORT and J. B. LAVIGNE, J. Amer. Chem. Soc. 75, 5329 (1953).
- 170. Y.K.SAWA, N.TSUIJI and S.MAEDA, Tetrahedron 15, 144, 154 (1961).
- 171. H.E. UNGNADE, Chem. Revs. 38, 407 (1946).
- 172. M. GATES, R. B. WOODWARD, W. F. NEWHALL and R. KÜNZLI, J. Amer. Chem. Soc. 72, 1141 (1950).

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- 173. M. GATES and W. G. WEBB, J. Amer. Chem. Soc. 80, 1186 (1958).
- 174. A. GRÜSSNER, J. HELLERBACH, A. BROSSI and O. SCHNIDER, Helv. Chim. Acta 39, 1371 (1956).
- 175. Y.K. SAWA, K.KAWASAKI and S. MAYEDA, Pharm. Bull. (Tokyo) 8, 960 (1960).
- 176. J. VON BRAUN, Ber. Deutsch. Chem. Ges. B. 47, 2312 (1914).
- 177. R.L. CLARK, A.A. PESSOLANO, J. WEIJLARD and K. PFISTER 3rd, J. Amer. Chem. Soc. 75, 4963 (1953).
- 178. A. GRÜSSNER, J. HELLERBACH and O. SCHNIDER, Helv. Chim. Acta 40, 1232 (1957).
- 179. J. HELLERBACH, A. GRÜSSNER and O. SCHNIDER, U. S. Pat. 2970147.
- 180. O. SCHNIDER, A. GRÜSSNER and J. HELLERBACH (unpublished).
- 181. S. SUGASAWA and S. SAITO, Pharm. Bull. (Tokyo) 4, 237 (1956).
- 182. S. SAITO, Pharm. Bull. (Tokyo) 4, 438 (1956).
- 183. M. PROTIVA, V. MYCHAJLYSZYN and J. O. JILEK, Chem. Listy 49, 1045 (1955).
- 184. M.S. NEWMAN and B.J. MAGERLEIN, J. Amer. Chem. Soc. 69, 942 (1947).
- 185. E.L. MAY and J.G. MURPHY, J. Org. Chem. 19, 615 (1954).
- 186. E. L. MAY and J. G. MURPHY, J. Org. Chem. 19, 618 (1954).
- 187. E. L. MAY, J. Org. Chem. 23, 947 (1958).
- 188. N.SUGIMOTO, J. Pharm. Soc. Japan 75, 183 (1955).
- 189. N. SUGIMOTO and S. OHSHIRO, Pharm. Bull. (Tokyo) 4, 353 (1956).
- 190. E. OCHIAI and K. HARASAWA, Pharm. Bull. (Tokyo) 3, 369 (1955).
- 191. K. HARASAWA, J. Pharm. Soc. Japan 77, 168, 172, 794 (1957).
- 192. N. SUGIMOTO and S. OHSHIRO, Pharm. Bull. (Tokyo) 4, 357 (1956).
- 193. N. SUGIMOTO, S. OHSHIRO, H. KUGITA and S. SAITO, Pharm. Bull. (Tokyo) 5, 62 (1957).
- 194. N. SUGIMOTO and S. OHSHIRO, Pharm. Bull. (Tokyo) 5, 316 (1957).
- 195. Jap. Pat. 3799/57.
- 196. N. SUGIMOTO and H. KUGITA, Pharm. Bull. (Tokyo) 5, 67 (1957).
- 197. N. SUGIMOTO and H. KUGITA, Pharm. Bull. (Tokyo) 6, 429 (1958).
- 198. Jap. Pat. 30213/57.
- 199. N. SUGIMOTO and S. OHSHIRO, Tetrahedron 8, 296 (1960).
- 200. S. OHSHIRO, Tetrahedron 8, 304 (1960).
- 201. S. OHSHIRO, Tetrahedron 10, 175 (1960).
- 202. N. SUGIMOTO and H. KUGITA, Pharm. Bull. (Tokyo) 3, 11 (1955).
- 203. N. SUGIMOTO and H. KUGITA, Pharm. Bull. (Tokyo) 5, 378 (1957).
- 204. H. KUGITA, Pharm. Bull. (Tokyo) 4, 29 (1956).
- 205. H.KUGITA, Pharm. Bull. (Tokyo) 4, 189 (1956).
- 206. O.Häfliger, A.Brossi, L.H. Chopard-dit-Jean, M. Walter and O.Schnider, *Helv. Chim. Acta* 39, 2053 (1956).
- 207. O. SCHAUMANN, Handbuch der experimentellen Pharmakologie Vol. XII, Springer Berlin, "Morphin- und morphinähnlich wirkende Verbindungen" (1957).
- 208. H.KRUEGER, N.B.EDDY and M.SUMWALI, "The Pharmacology of the Opium Alkaloids" Suppl. 165 to the Public Health Reports, US Government Printing Office, Washington (1941).
- 209. M.H. SEEVERS, J. Pharmacol. Exp. Therap. 51, 141 (1934).
- 210. M.H. SEEVERS, J. Pharmacol. Exp. Therap. 56, 147 (1936).
- 211. M.H. SEEVERS, Ann. N.Y. Acad. Sci. 51, 98 (1948).
- 212. L.A. WOODS, J.B. WYNGAARDEN and M.H. SEEVERS, Proc. Soc. Exp. Biol. Med. 65, 113 (1947).
- 213. N. B. EDDY and J. G. REID, J. Pharmacol. Exp. Therap. 52, 468 (1934).
- 214. J.H. PIERCE and O.H. PLANT, J. Pharmacol. Exp. Therap. 31, 212 (1927).
- 215. S. KAYMAKCALAN and L.A. WOODS, J. Pharmacol. Exp. Therap. 117, 112 (1956).
- 216. E. KOMLÓS and J. FÖLDES, Arch. Exp. Pathol. u. Pharmakol. 229, 463 (1956).
- 217. P.O. WOLFF, Deutsch. Med. Wchschr. 81, 57 (1956).
- 218. National Institute of Mental Health Service, Hospital at Lexington (Kentucky/USA).

- 218a. H. Isbell and H. FRASER, Bull. Narc. 14, 25 (1962).
- 219. L.KOLB and C.K.HIMMELSBACH, Amer. J. Psychiat. 94, 759 (1938).
- 220. N.B.EDDY, H. BESENDORF and B. PELLMONT, Bull. Narcotics U.N. 10, 23 (1958).
- 221. N.B. EDDY and D. LEIMBACH, J. Pharmacol. Exp. Therap. 107, 385 (1953).
- 222. F. GROSS, Helv. Physiol. et Pharmacol. Acta 5, C.31 (1947).
- 223. J.D.HARDY, H.G. WOLFF and H. GOODELL, J. Clin. Invest. 19, 649 (1940).
- 224. J.D.HARDY, H.G.WOLFF and H. GOODELL, Amer. J. Physiol. 126, 523 (1939).
- 225. H.G. WOLFF, J.D. HARDY and H. GOODELL, J. Pharmacol. Exp. Therap. 75, 38 (1942)
- 226. N. ERCOLI and M. N. LEWIS, J. Pharmacol. Exp. Therap. 84, 301 (1945).
- 227. W. Koll and H. REFFERT, Arch. Exp. Pathol. u. Pharmakol. 190, 687 (1938).
- 228. T. GORDONOFF and K. RUCKSTUHL, Dissertation, Bern (1939).
- 229. K. FROMHERZ, Arch. intern. Pharmacodyn. 85, 387 (1951).
- 230. W. M. BENSON, P. L. STEFKO and L. O. RANDALL, J. Pharmacol. Exp. Therap. 109, 189 (1953).
- 231. M.B. SLOMKA and E.G. GROSS, Proc. Soc. Exp. Biol. Med. 81, 548 (1952).
- 232. M.B.SLOMKA and C.K.SLEETH, Proc. Soc. Exp. Biol. Med. 84, 532 (1953).
- 233. N.B.EDDY, H.HALBACH and O.J.BRAENDEN, Bull. World Health Organ. 14, 353 (1956).
- 234. A. CREHAN and J. IRISH, Med. Ass. 34, 74 (1954).
- 235. H.K. VON RECHENBERG and R.ZEERLEDER, Schweiz. Med. Wchschr. 81, 1086 (1951).
- 236. R.D. HUNT and F.F. FOLDES, New England J. Med. 248, 803 (1953).
- 237. M.Bozza, Minerva Chir. (Torino) 9, 319 (1954).
- 238. E.G.GROSS and WM.K.HAMILTON, J. Lab. Clin. Med. 43, 938 (1954).
- 239. J. BECKER and O. BUNDSCHUH, Med. Klin. 47, 546 (1952).
- 240. O.SCHRAPPE and W.BERG, Arzneimittel-Forsch. 9, 507 (1959).
- 241. C. QUAGLIA and L. G. FRANCO, Gazz. med. ital. 113, 297 (1954).
- 242. H. ISBELL and H.F. FRASER, J. Pharmacol. Exp. Therap. 107, 524 (1953).
- 243. N.B. EDDY, J. Amer. Geriatrics Soc. 4, 177 (1956).
- 244. N.B.EDDY, H.HALBACH and O.J.BRAENDEN, Bull. World Health Organ. 17, 684 (1957).
- 245. E.R. HART, J. Pharmacol. Exp. Therap. 72, 19 (1941).
- 246. J. WEIJLARD and A. E. ERICKSON, J. Amer. Chem. Soc. 64, 869 (1942).
- 247. K. FROMHERZ and B. PELLMONT, Experientia 8, 394 (1952).
- 248. B. PELLMONT and H. BESENDORF, Anaesthesist 6, 74 (1957).
- 249. H. BRÄUNLICH and H. HOFMANN, Arzneimittel-Forsch. 12, 174 (1962).
- 250. H.F. FRASER and H.ISBELL, Fed. Proc. 14, 340 (1955).
- 251. G. MALORNY and F. K. OHNESORGE, Arch. Exp. Pathol. u. Pharmakol. 225, 80 (1954).
- 252. G. MALORNY, Arzneimittel-Forsch. 5, 252 (1955).
- 253. W. M. BENSON, E. O'GARA and S. VAN WINKLE, J. Pharmacol. Exp. Therap. 106, 373 (1962).
- 254. W.K. HAMILTON and S. C. CULLEN, Anesthesiology 14, 353 (1953).
- 255. D. V. THOMAS and S. M. TENNEY, J. Pharmacol. Exp. Therap. 113, 250 (1955).
- 256. C.M. LANDMESSER, P.F. FORMEL and J.G. COUVERSE, Anesthesiology 16, 520 (1955).
- 257. M.SCHWAB, H.M.BECKER, E.KÖPPEN, M.PODWORNY and P.H.WAGNER, Arzneimittel-Forsch. 7, 283 (1957).
- 258. F.F. Foldes and Th.S. MACHAJ, Anaesthesist 6, 95 (1957).
- 259. M.Swerdlow, F.F.Foldes and E.S.Siker, Amer. J. Med. Sci. 230, 237 (1955).
- 260. O. MEYER and H.OCHMIG, Anaesthesist 5, 4 (1956).
- 261. U. WILBRAND and P. MATTHAES, Zschr. ges. exp. Med. 130, 354 (1958).
- 261a. R.C.BALAGOT, M.S.SADOVE and O.SUGAR, J. Intern. Coll. Surgeons 35, 330 (1961).
- 261b. M.S. SADOVE and M.H. SCHIFFRIN, Postgrad. Med. 29, 346 (1961).
- 261c. W. U. REIDT, J. H. CULLEN and L. H. E. SMITH, Am. Rev. Respirat. Dis. 83, 481 (1961).
- 261d. E. HOCHULI, Therap. Umsch. 18, 299 (1961).

- 261 e. A.S.KEATS, Brit. J. Anaesthesia 33, 168 (1961).
- 261f. G. Hossli, Brit. J. Anaeshesia 33, 169 (1961).
- 261g. J.P. MCENVA, Brit. Med. J. 1, 1763 (1961).
- 262. M. Swerdlow, Anaesthesia 13, 318 (1958).
- 263. M. ZINDLER and P. GANZ, Deutsch. Med. Wchschr. 80, 410 (1955).
- 264. W. HART and F. BECKER, Anaesthesist 10, 230 (1961).
- 265. W.SCHAUMANN, Arch. Exp. Pathol. u. Pharmakol. 233, 112 (1958).
- 266. M. SWERDLOW, F.F. FOLDES and E.S. SIKKER, Brit. J. Anaesthesia 27, 244 (1955).
- 267. G.GRIESSER, Klin. Wchschr. 35, 851 (1957).
- 268. G. GRIESSER, Zbl. Chir. 82, 1009 (1957).
- 269. H.SCHNIEDEN, Brit. J. Pharmacol. 15, 510 (1960).
- 270. H.SCHNIEDEN and E.K.BLACKMORE, Brit. J. Pharmacol. 10, 45 (1955).
- 271. G. HOSSLI and G. BERGMANN, Schweiz. Med. Wchschr. 89, 863 (1959).
- 272. H. CULLUMBINE and T.S. KONOP, Can. J. Biochem. and Physiol. 37, 1075 (1959).
- 273. K. KJELLGREN, Brit. J. Anaesthesia 32, 2 (1960).
- 274. E.A. GAENSLER, J. M. MCGOWAN and F. F. HENDERSON, Surgery 23, 211 (1948).
- 275. A. KALLENBERG, Münch. Med. Wchschr. 101, 510 (1959).
- 276. A. IMBESI, Att. Soc. Perlorit. Sci. Fis. Mat. Natur. 5, 8 (1958/1959).
- 277. K.H.CHEMNITIUS, R.SCHROEDER and H.HOFMANN, Zschr. ges. exp. Med. 134, 372 (1961).
- 278. F.SCHULTZE-GÖRLITZ, Nervenarzt 30, 256 (1959).
- 279. S. WIESER, Wien. Med. Wchschr. 110, 719 (1960).
- 280. Bull. Stupef. 8, 39 (1957).
- 281. M.P.ENGELMEIFR, Med. Klin. 1784 (1955).
- 282. L. TABORSKY, Wien. Med. Wchschr. 108, 220 (1958).
- 283. United States Public Health Service Hospital, Lexington (Kentucky, U.S.A.).
- 284. N.B.EDDY, M.PILLER, L.A.PIRK, O.SCHRAPPE and S.WENDE, Bull. Narcotics U.N. 12, 1 (1960).
- 285. S. WENDE, Arch. Exp. Pathol. u. Pharmakol. 228, 168 (1956).
- 286. H. Isbell, Merck Rept. April (1953).
- 287. M. PILLER and D. LASZLO, Schweiz. Med. Wchschr. 90, 518 (1960).
- 288. P. PULOS, A. BERNSTEIN and L. PERTMAN, Illinois Med. J. 101, 87 (1955).
- 289. K. FROMHERZ and B. PELLMONT (unpublished).
- 290. D.A. RAO and H. HOFMANN, Experientia 18, 7 (1962).
- 291. J. TELFORD, C. N. PAPADOPOULOS and A. S. KEATS, J. Pharmacol. Exp. Therap. 133,106 (1961).
- 292. K. FROMHERZ (unpublished).
- 293. J.H.HUNT and M.J.LINETT, Brit. Med. J. 1, 1723 (1960).
- 294. G. MALORNY, Regensburg Jb. ärztl. Fortbldg. 8, 183 (1960).
- 295. W. HÖRTNAGL, Wien. Klin. Wchschr. 69, 506 (1957).
- 296. E. ZIEHME, Kinderärztl. Praxis 28, 101 (1960).
- 297. E. HOCHULI and O. KÄSER, Therap. Umsch. 11, 79 (1954).
- 298. E. HOCHULI, Schweiz. Med. Wchschr. 87, 1327 (1957).
- 299. R. ULM, Wien. Klin. Wchschr. 72, 929 (1960).
- 300. K. LOEW, Wien. Klin. Wchschr. 72, 898 (1960).
- 301. W. K. HAMILTON and S. C. CULLEN, Anesthesiology 14, 550 (1953).
- 302. E. SIKER, Brit. Med. J. 1326 (1956).
- 303. P. RADNAY, J. Intern. Coll. Surgeons 26, 155 (1956).
- 304. V. K. STOELTING and M. L. HICKS, Can. Anaes. Soc. J. 3, 107 (1956).
- 305. TH. S. MACHAJ and F. F. FOLDES, Penn. Med. J. 59, 571 (1956).
- 306. F.F. FOLDES, E. LIPSCHITZ, G. M. WEBER, M. SWERDLOW and L. A. PIRK, J. Amer. Med. Assoc. 160, 168 (1956).
- 307. G. MAY, M. PHILLIPS and J. ADRIANI, Anesthesiology 18, 871 (1957).

- 308. F.F. FOLDES and K.H. ERGIN, J. Amer. Med. Assoc. 166, 1153 (1958).
- 309. A.R. HUNTER, Brit. J. Anaesthesia 30, 234 (1958).
- 310. M. Swerdlow, Anaesthesia 13, 318 (1958).
- 311. M. Swerdlow, Acta Anaesthesiol. Belgica 25 (1958).
- 312. M. SWERDLOW, Anaesthesia 14, 178 (1959).
- 313. K. GOTO, H.YAMASAKI and J.YAMAMOTO, Proc. Jap. Acad. 33, 660 (1957).
- 314. K. TAKAGI, H. FUKUDA, M. WATANABE and M. SATO, J. Pharm. Soc. Japan 80, 1506 (1960).
- W. M. BENSON, P. L. STEFKO and L. O. RANDALL, J. Pharmacol. Exp. Therap. 109, 189 (1953).
- 316. B. PELLMONT and H. BÄCHTOLD, Schweiz. Med. Wchschr. 84, 1368 (1954).
- 317. P.L. STEFKO and W.M. BENSON, J. Pharmacol. Exp. Therap. 103, 363 (1951).
- 318. P.L. STEFKO and W.M. BENSON, J. Pharmacol. Exp. Therap. 108, 217 (1953).
- 319. P.KRÖPFLI, Helv. Physiol. et Pharmacol. Acta 8, 33 (1950).
- 320. P.L. STEFKO and J. DENZEL, J. Pharmacol. Exp. Therap. 119, 185 (1957).
- 321. R. DOMENJOZ, Arch. Exp. Pathol. u. Pharmakol. 215, 19 (1952).
- 322. E.M. BOYD, R.N. HICKS and A.V. TRAINOR, Arch. intern. Pharmacodyn. 424 (1956).
- 323. H. BÄCHTOLD (unpublished).
- 324. H. Isbell and H. F. FRASER, J. Pharmacol. Exp. Therap. 106, 397 (1952).
- 325. L.J. CASS and W.S. FREDERIK, New Engl. J. Med. 249, 132 (1953).
- 326. L.J. CASS and W.S. FREDERIK, J. Lab. Clin. Med. 48, 879 (1956).
- 327. L.J. CASS, W.S. FREDERIK and J.B. ANDOSCA, Amer. J. Med. Sci. 227, 291 (1954).
- 328. G. CAPELLO and S. DI PASQUALE, Schweiz. Z. Tuberk. 12, 80 (1955).
- 329. H.A. BICKERMAN, E. GERMAN, B. M. COHEN and S.E. ITKIN, Amer. J. Med. Sci. 234, 191 (1957).
- 330. G. BUCHEGGER and P. FRISCH, Med. Klin. 1846 (1954).
- 331. A. HOTTINGER, Schweiz. Med. Wchschr. 84, 1372 (1954).
- 332. J.STEIGER, Praxis 44, 1081 (1955).
- 333. F.K. TÜNNERHOFF and H.K. SCHWABE, Klin. Wchschr. 33, 576 (1955).
- 334. N. RALPH, Amer. J. Med. Sci. 227, 297 (1954).
- 335. A. KUMMER, Praxis 44, 132 (1955).
- 336. H. MAURER, Deutsch. Med. Wchschr. 80, 351 (1955).
- 337. G.ZETTEL, Ärztliche Praxis 7, 9 (1955).
- 338. E. HASLREITFR, Zbl. Aerosol. Forsch. 10, 135 (1962).
- 339. G. GRAFE, Med. Welt, 1741 (1958).
- 340. G. GUIDI and F. GARDIN, Giorn. Gerontol. 5, 867 (1957).
- 341. SINOMENINE, Shionogi & Co. Osaka/Japan.
- 342. SHIGERU TAKAORI, Deutsch. Med. Wchschr. 62, 1634 (1936).
- 343. R. JÜRGENS and H. BÄCHTOLD (unpublished).
- 344. A. SELYE, Can. Med. Assoc. J. 61, 553 (1949).
- 345. J.SEIFTER, D.H.BAEDER and A.J.BEGANY, Proc. Soc. Exp. Biol. Med. 72, 277 (1949).
- 346. P.M. L. OESTEREICHER, C.G. FARMILO and L. LEVI, Bull. Narcotics U.N. 6, (3, 4) 42 (1954).
- 347. L. LEVI, C. E. HURLEY and R. A. HINGS, Bull. Narcotics U.N. 7, (1) 42 (1955).
- 348. W.H.BARNES, Bull. Narcotics U.N. 6 (1), 20 (1954).
- 349. W. H. BARNES and H. M. SHEPPARD, Bull. Narcotics U.N. 6 (2) 27 (1954).
- 350. C.G.FARMILO, L.LEVI, P.M.L.OESTEREICHER and R.J.Poss, Bull. Narcotics U.N. 4, (4) 16 (1952).
- 351. L. LEVI, Bull. Narcotics U.N. 7 (3, 4) 43 (1955).
- 352. C.G. FARMILO and L. LEVI, Can. J. Chem. 30, 782 (1952).
- 353. E. VIDIC, Arzneimittel-Forsch. 3, 34, 490 (1953).
- 354. J. BREINLICH, Arzneimittel-Forsch. 3, 93, 212, 490 (1953).
- 355. L. ROSENTHALER and F. LÜDY-TENGLR, Plurm. Zentralialle 99, 473 (1960).

- 356. B.B.BRODIE, S. UDENFRIEND and W. DILL, J. Biol. Chem. 168, 335 (1947).
- 357. H. KAISER and H. JORI, Pharm. Ztg. Nachr. 87, 963 (1952).
- 358. H. KAISER and H. JORI, Arch. Pharm. 287, 224 (1954).
- 359. H. JATZKEWITZ, Hoppe-Seyler's Z. physiol. Chem. 292, 94 (1953).
- 360. H. JATZKEWITZ, Deutsch. Med. Wchschr. 79, 541 (1954).
- 361. A.S. CURRY and H. POWELL, Nature 173, 1143 (1954).
- 362. A. BROSSI, O. HÄFLIGER and O. SCHNIDER, Arzneimittel-Forsch. 5, 62 (1955).
- 363. E. VIDIC, Arzneimittel-Forsch. 5, 291 (1955).
- 364. E. VIDIC, Arzneimittel-Forsch. 7, 314 (1957).
- 365. G. WAGNER, Pharmazie 10, 470 (1955).
- 366. R.BONNICHSEN, A.C.MAEHLY and S.NORDLANDER, Acta Chem. Scand. 11, 1280 (1957).
- 367. R. FISCHER and N. OTTERBECK, Scientia Pharmaceutica 25, 242 (1957).
- 368. K. WILLNER, Arch. Toxikol. 17, 347 (1959).
- 369. M. BRANDSTÄTTER-KUNERT, A. KOFLER and O. KOSTENZER, *Scientia Pharmaceutica* 28, 7 (1960).
- 370. E.G.C.CLARKE, J. Pharm. Pharmacol. 10, 642 (1958).
- 371. E.G.C. CLARKE, Bull. Stupef. 11, 28 (1959).
- 372. L.A. WOODS, L.B. MELLET and K.S. ANDERSEN, J. Pharmacol. Exp. Therap. 124, 1 (1958).
- 373. C.H. MARCH and H.W.ELLIOT, Proc. Soc. Exp. Biol. Med. 86, 494 (1954).
- 374. H.W. ELLIOT, B.M. TOLBERT, T.K. ADLER and H.H. ANDERSON, Proc. Soc. Exp. Biol. Med. 85, 77 (1954).
- 375. T.K. Adler, J. Pharmacol. Exp. Therap. 106, 371 (1952).
- 376. T.K. ADLER, J. Pharmacol. Exp. Therap. 110, 1 (1954).
- 377. T.K. ADLER, J. M. FUJIMOTO and E. L. WAY, J. Pharmacol. Exp. Therap. 113, 1 (1955).
- 378. T. K. ADLER, J. M. FUJIMOTO, E. L. WAY and E. M. BAKER, J. Pharmacol. Exp. Therap. 114, 251 (1955).
- 379. N.P. PLOTNIKOFF, H. W. ELLIOT and E. L. WAY, J. Pharmacol. Exp. Therap. 104, 377 (1952).
- 380. N. P. PLOTNIKOFF, J. Pharmacol. Exp. Therap. 113, 44 (1955).
- 381. N. P. PLOTNIKOFF, Fed. Proc. 14, 379 (1955).
- 382. J. J. BURNS, B.L. BERGER, P.A. LIEF, A. WOLLACK, E. M. PAPPER and B. B. BRODIE, J. Pharmacol. Exp. Therap. 114, 289 (1955).
- 383. G.J. MANNERING and L.S. SCHANKER, J. Pharmacol. Exp. Therap. 124, 296 (1958).
- 384. G.J. MANNERING and L.S. SCHANKER, J. Pharmacol. Exp. Therap. 119, 164 (1957).
- 385. H. RAPOPORT and S. MASAMUNE, J. Amer. Chem. Soc. 77, 6359 (1955).
- 386. A.E. TAKEMORI and G.J. MANNERING, J. Pharmacol. Exp. Therap. 123, 171 (1958).
- 387. J. AXELROD, J. Pharmacol. Exp. Therap. 117, 322 (1956).
- 388. J. AXELROD, Science 124, 263 (1956).
- 389. G.J. MANNERING and A.E. TAKEMORI, J. Pharmacol. Exp. Therap. 127, 187 (1959).
- 390. H.J. CHERNOV, J.W. MILLER and G.J. MANNERING, Fed. Proc. 18, 376 (1959).
- 391. H. HERKEN, D. NEUBERT and R. TIMMLER, Arch. Exp. Pathol. u. Pharmakol. 237, 319 (1959).

PART IIB. 6,7-Benzomorphans

ΒY

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Introduction

SINCE 1925, when the fundamental molecular structure of morphine (1) became known with reasonable certainty⁽¹⁾ various portions of the molecule have been fashioned by synthesis. A significant contribution in this respect, (-)-3-hydroxy-*N*-methyl-morphinan (Levorphanol, 2) resulted from one of the earliest attempts at the total synthesis of morphine itself. Levorphanol, a member of the morphinan (3) family, (Part IIA) although lacking the oxygen bridge, the alcoholic hydroxyl and the alicyclic double bond of morphine is nevertheless three to four times more potent than morphine with no greater, perhaps less, harmful side effects at optimal doses⁽²⁾. This favourable, if unexpected, result provided optimism that the molecule might be still further simplified without undue loss of analgesic activity and with, perhaps, reduction of deleterious effects – in short, with some dissociation of beneficial and harmful actions.

However, when the present study was projected in 1951, it was the consensus that several structural features of morphine and the morphinans should



be embodied in any modifications of these molecules obtained by synthesis. They are, (a) the benzene nucleus; (b) the quaternary carbon (C-13 of compound 3) attached to this nucleus; and (c) the tertiary nitrogen two methylene groups removed from the quaternary carbon. The view was also held that the tertiary nitrogen should be in six-membered ring formation and methyl-substituted as in 1 and 2 in which case the phenolic hydroxyl located *meta* to the quaternary carbon attachment should indeed be advantageous.⁽³⁾

INTRODUCTION

Finally, optical resolution of any racemate necessarily obtained in ordinary chemical syntheses could be expected to give one analgesically active, one relatively inactive antipode — in effect, a two-fold enhancement of activity. These structural considerations are depicted in formula 5 and have served as a guide in the syntheses herein described.



Two main lines of approach have been followed in variations from 3hydroxy-N-methylmorphinan (2) which, like morphine, is in essence a 5,6,7,8,9,10,13,14-octahydrophenanthrene containing an iminoethano system *cis*-fused to the 13 and 9-positions. The first of these approaches involved a molecule that would result from elimination of the 9,10-bridge carbons and relocation of nitrogen closure from position 9 to 8. Such a change produces phenylcyclohexane derivatives (6) or phenylmorphans⁽⁴⁾. In the second line of attack, a series of compounds has evolved the simplest of which would result from excision of carbons 6, 7 and 8 of ring C of (2) with retention of carbon 5 of (2) to preserve the quaternary character of carbon 13. The resultant entity (7) is a hydronaphthalene still containing the *cis*-fused iminoethano system typical of morphine and 3-hydroxy-*N*-methyl-morphinan. This entity and its many derivatives are called briefly 6,7-benzomorphans (see formula 4). It should be noted that the numbering of the positions in this series is different from that of morphine and morphinan.



FIG. 1

CHAPTER III

Chemistry of 6,7-Benzomorphans

1. 5-Alkyl-2(N)-methyl-6,7-benzomorphans (only hydrogen at position 9)

The simplest (model) compound of the benzomorphan series, 2,5-dimethyl-6,7-benzomorphan, (9) was synthesized in three different ways. In the first and longest method, ⁽⁵⁾ hydratroponitrile (8) was the starting substance from which both the hydroaromatic and heterocyclic rings of (9) needed to be constructed. Ten relatively straightforward steps were required as shown in Fig. 2. The overall yield was about 5 per cent. The second route, with a start-



ing compound 3,4-dihydro-1-methyl-2(1*H*) naphthalenone (13) already containing the tetrahydronaphthalene skeleton of (9) initially gave lower yields⁽⁵⁾ than the longer method. However, significant improvement of the shorter sequence was subsequently achieved[†] (see also ref. 19). This method of synthesis was first reported by BARLTROP⁽⁶⁾ who suggested the name 6,7-benzmorphan (later changed to benzomorphan by the editors of the Journal of Organic Chemistry) for a class of compounds corresponding to (4). BARLTROP used 2-chloro-*N*,*N*-diethylethylamine rather than the *N*,*N*-dimethyl derivative in the alkylation of (13) and did not take his synthesis beyond the stage represented by the quaternary compound (12).



0.1 R=Me 0.4 R=Me, R_1 =H 0.7 R=Et, R_1 =OMe 0.9 R=Pr, R_1 =OMe 0.2 R=Et 0.5 R=Me, R_1 =OMe 0.8 R=Et, R_1 =OH 0.10 R=Pr, R_1 =OH 0.3 R=Pr 0.6 R=Me, R_1 =OH

Finally, (9, 19.4) has been obtained from 1,4-dimethylpyridinium iodide (14.1) as shown in Fig. 3. In this instance (14.1) and benzylmagnesium chloride were brought to reaction (sequence I) in ether to give the rather unstable dihydro compound (15.4). This was reduced with palladium-barium sulphate-catalyzed hydrogen⁽⁷⁾ or preferably with sodium borohydride to the tetrahydro derivative (16.4) which could be cyclized with either 48 per cent hydrobromic acid or 85 per cent phosphoric acid. This sequence of reactions will be recognized as an application of the Grewe morphinan synthesis (Part A). The fact that (9, 19.4) could be prepared by the three methods described above is considered to be ample proof of its structure.

The 2'-hydroxy relative $(10)^{(7)}$ of (9) was first obtained via nitration of (9), hydrogenation of the resultant 2'-nitro compound and diazotization of the

† E.M.FRY (unpublished).

2'-amino derivative. In addition, (10) or (19.6) has been totally synthesized from 3,4-dihydro-7-methoxy-1-methyl-2(1*H*) naphthalenone (11)⁽⁸⁾ in the same manner as described for (9) from (13) (Fig.2) and from γ -picoline methiodide or methobromide (14.1) and *p*-methoxybenzylmagnesium chloride (sequence I, Fig.3)⁽⁷⁾,[†] Alternatively^(9,11), (14.1) was reduced (sequence II) to 1,4-dimethyl-1,2,5,6,-tetrahydropyridine (17.1) which was quaternized to (18.5) with *p*-methoxybenzyl chloride. Treatment of (18.5) with ethereal phenyllithium caused rearrangement of the *p*-methoxybenzyl radical from nitrogen to adjacent carbon of the pyridine moiety (STEVENS rearrangement)⁽⁹⁾ giving 2-*p*-methoxybenzyl-1,4-dimethyl-1,2,5,6,-tetrahydropyridine (16.5) identical with that encountered in sequence I. Cyclization of (16.5) affordcd (19.6), *O*-demethylation occurring simultaneously with ring closure. By sequence II, 5-ethyl- (19.8)⁽¹⁰⁾, and 5-propyl- (19.10)⁽¹¹⁾ 2'-hydroxy-2methyl-6,7-benzomorphans have been synthesized from (14.2) and (14.3) in overall yields of 20-30 per cent.

2. α - and β -5,9-Dialkyl-2(N)-methyl-6,7-benzomorphans

In comparing some of the more intimate structural features of 2'-hydroxy-2,5-dimethyl-6,7-benzomorphan (10, 19.6) with 3-hydroxy-*N*-methylmorphinan (2), one observes that stereochemically, (10) mimics (2) at asymmetric carbons 5 and 1 (13 and 9 in compound 2). The introduction of a methyl group at position 9 of compound 10 would provide a third asymmetric centre and would afford the molecule, 2'-hydroxy-2,5,9-trimethyl-6,7-benzomorphan (20) in which there is complete stereochemical approximation of (2).



Attempts to synthesize such a compound without the phenolic hydroxyl, 2,5,9-trimethyl-6,7-benzomorphan, (23) from the methyl ketone (22) by the method outlined in Fig.2 were fruitless⁽¹²⁾.



† E. M. FRY, J. H. AGER and E. L. MAY (unpublished).



It was found possible to obtain (23) and the 2'-hydroxy relative (20, 29.3) from 1,3,4-trimethylpyridinium bromide or iodide (24) again by application of the GREWE morphinan synthesis (sequence I) or by the method based on the STEVENS rearrangement (sequence II, Fig.4) as described previously for



5(mono)-alkyl analogues. The yield of $(29.1)^{(13)}$ was about the same as that of $(29.3)^{(13,14)}$ [20 per cent based on (24)] in sequence I. In sequence II, however, the overall yield of $(29\cdot1)$ was markedly lower (only 6.5 per cent), the difference being in the rearrangement step $(28-26)^{(9)}$. As described before in the 5(mono)-alkyl series (Fig.2), compound (29.1) could be converted in three steps to (29.3). Nuclear magnetic resonance spectra served to establish the position of the double bond in the borohydride reduction products (27) and $(17)^{(9)}$.

For confirmation of the fundamental skeleton of (29), 2,5,9-trimethyl-6,7benzomorphan (29.1) was degraded $^{(13)}$ to 1,2-dimethylnaphthalene (31.1) (indistinguishable from authentic material) by exhaustive methylation and palladium-charcoal aromatization of the resulting methine (30.1) or its dihydro derivative. Similarly (29.2), prepared from (29.3) by methylation with ethereal diazomethane, gave 7-methoxy-1,2-dimethylnaphthalene (31.2)⁽¹⁴⁾.

Utilizing the two methods outlined in Fig. 4, the following 3,4-dialkyl-1methylpyridinium bromides and/or iodides (32) have been converted (cf. Fig. 5) to 5,9-dialkyl-2'-hydroxy-6,7-benzomorphans: 3,4-dimethyl;^{9,14)} 3,4-





diethyl;^(9,15) 3,4-dipropyl;⁽¹¹⁾ 3-ethyl-4-methyl;⁽¹⁶⁾ 3-methyl-4-ethyl;⁽¹⁶⁾ 3-methyl-4-propyl.† The predominant product (65-75 per cent yields and arbitrarily designated α) obtained in the acid cyclization of (33) has been shown (*vide infra*) to conform to the structure and stereochemistry represented by (34). In all instances but one (cyclization of (33.6)†) a small yield (5-8 per cent) of an isomeric product was isolated. The latter (designated β) proved to be diastereoisomeric (at C-9) with the α -isomers by degradation of two representatives (35.1 and 35.2) to 1,2-dimethyl- and 1,2-diethyl-7-methoxy-naphthalenes (36.1 and 36.2) respectively^(14,16), identical with those obtained from the corresponding (34.1) and (34.2).

† J.H. AGER (unpublished).

That the stereochemistry of the predominant (α) products and the lesser diastereomers (β) is accurately represented by (34) and (35) respectively, in addition to having been predicted by theory⁽¹³⁾, has been demonstrated by methiodide reaction-rate data⁽¹⁷⁾. Quaternization of the α -compounds with methyl iodide occurred from five to ten times as rapidly as the β -counterparts. This could only mean that in the α compounds the 9-alkyl substituent is oriented away from the nitrogen (axial for the hydroaromatic ring) of the iminoethano system (34) geometrically constrained to a cis(diaxial)-fusion as in morphine (1) and the morphinans (2). The slower-reacting β compounds must therefore be assigned structure (35) in which the 9-alkyl substituent, equatorially oriented for the hydroaromatic ring, is close enough to the nitrogen to cause steric hindrance. It was noted in the rate studies⁽¹⁷⁾ that, as the size of R_1 increased in the β series, reaction with methyl iodide became slower. This, then, related the α compounds (34) with their *cis*-juxtaposed (for the hydroaromatic ring) 5,9-dialkyl groups, to morphine and the morphinans whose cis-fusion of rings B and C is a certainty (see Part IIA).

Further confirmation of these configurational assignments was observed in nuclear magnetic resonance spectra of the 5,9-dimethyl compounds (34.1 and 35.1)⁽¹⁷⁾. Thus the 9-methyl frequencies (doublet) of the α -isomer are at higher field (about 25 c/s) than those of the β -isomer attributable to aromatic ring current effects. This is possible in structure (34.1), not (35.1).

As will be shown in the pharmacological discussion, the scarce β -isomers are from five to seventy times more potent as analgesic agents than their α counterparts. The β bases are also lower melting and more soluble in acctone than the α bases. In three of the five pairs of diastereoisomers isolated, there were distinct infrared spectral differences, particularly in the 6-6.5 μ region. A comparison of some of these properties which were most helpful in separation procedures is given in Table XVIII.

3. α - and β -9-Hydroxy-2(N)-methyl-6,7-benzomorphans

The substitution of a hydroxyl group at position 14 of morphine-like structures generally has an enhancing effect on analgesic activity. For example, 14-hydroxydihydrocodeinone (oxycodone) (37.1) and 14-hydroxydihydromorphinone, (oxymorphone) (37.2) are from two to four times as potent as dihydrocodeinone (hydrocodone) (38.1) and dihydromorphinone



2'-Hydroxy-2-methyl- 6,7-benzomorphan	Melting point °C	$\lambda_{\max}^{\operatorname{Nujol}}\left(\mu ight)$
1. α-5,9-Dimethyl	233-236	6.15, 6.33
2. β -5,9-Dimethyl	217-218	6.15, 6.33
3. a-5-Methyl-9-ethyl	219-223	6.16, 6.33
4. β -5-Methyl-9-ethyl	186–188	6.16, 6.33
5. α-5-Ethyl-9-methyl	249–254	6.16, 6.31
6. β -5-Ethyl-9-methyl	189–193	6.19
7. α-5,9-Diethyl	248-249	6.15, 6.31
8. β -5.9-Diethyl	214-215	6.20
9. a-5,9-Dipropyl	209-211	6.15, 6.31
10. β -5,9-Dipropyl	197–198	6.19

Table XVIII. Comparison of melting point and infrared spectral data of α - and β -5,9-dialkyl-2'-hydroxy-2-methyl-6,7-benzomorphans

(hydromorphone) (38.2) respectively^(1B). A similar modification of the basic benzomorphan structures (9), (10) and derivatives is represented by (39).

Appropriate starting materials for the synthesis of compounds of structure (39) were 2,5-dimethyl-9-oxo-6,7-benzomorphan methobromide (40.1)⁽⁵⁾ and the 2'-methoxy relative (40.2)⁽⁸⁾. When each (Fig. 6) was brought to reaction



with ethereal methylmagnesium iodide, 9-methyl carbinols of the structure and configuration shown in $(42.5)^{(19)}$ and $(42.7)^{(20)}$ were obtained in 75 per cent yield after pyrolytic extrusion of methyl bromide or iodide from the

intermediates (41.5) and (41.7) respectively. On the other hand, addition of methylmagnesium iodide or methyl-lithium to the bases (44.1) and (44.2) occurred in the reverse manner to give the methyl carbinols (45.5)⁽¹⁹⁾ and $(45.7)^{(20)}$. The assignment of an equatorial (for the hydroaromatic ring) conformation to the 9-hydroxyl substituent of (42.5) and (42.7) (designated α for convenience) and an axial arrangement for (45.5) and (45.7) (called β isomers) was based principally on infrared spectral measurements. With the α -isomers was noted a maximum at 3450 cm⁻¹ indicative of strong OH----N bonding, to be expected when the hydroxyl is oriented toward the nitrogen of the *cis*, diaxial fused iminoethano system as in (42.5) and (42.7). The β isomers, however, gave spectra clearly indicating OH--- π bonding, compatible with structures (45.5) and (45.7). Furthermore, double Hofmann degradation (followed by hydrogenation)⁽²¹⁾ of (42.5)⁽¹⁹⁾ and (42.7)⁽²⁰⁾ produced nitrogen-free products of the structures (43.5) and (43.7) respectively (cis-fusion of hydrofurano and hydroaromatic rings) as determined by spectral data and an alternative, relatively unambiguous synthesis⁽²²⁾ of (43.5). Compounds (45.5) and (45.7) gave nitrogen-free products having spectral characteristics which are accomodated by structures (46.5) and (46.7) (transfusion of the two hydrogenated rings.) Thus structures (42) conform to the oxymorphone (37.2)⁽²³⁾ and oxycodonc (37.1) stcreochemistry^(23,24).

This same stereochemical pattern of addition was followed by platinumoxide-catalyzed hydrogen. Thus (40.1) and (40.2) yielded through (41.4) and (41.6), (42.4)⁽¹⁹⁾ and (42.6)⁽²⁵⁾ respectively, while (44.1) and (44.2) gave (45.4)⁽¹⁹⁾ and (45.6)⁽²⁵⁾. Furthermore, changing R₁ to ethyl made no difference in the stereochemistry of the products (although the additions were markedly slower due to steric effects) and (40.3) led ultimately to (42.10) and (42.11), whereas (44.3) yielded (45.10) and (45.11)⁽²⁶⁾. Finally, neither ethylnor propylmagnesium iodide or bromide could be induced to add to the carbonyl group of (40.2) although a small yield of hydrogenation product (42.6) could be isolated in each instance⁽²⁶⁾. However, the less hindered carbonyl group of (44.2) received ethylmagnesium bromide to give the β -carbinol (45.14)⁽²⁶⁾.

The direction of addition to the carbonyl function of the above 9-oxobenzomorphans appears, therefore, to depend principally upon the electrical environment of the neighbouring nitrogen. When the nitrogen is cationic (40), carbinols are formed with hydroxyl oriented toward it. With negative nitrogen (44) the additions are reversed in stereochemistry. Within the narrow limits of the study, increased steric hindrance has retarded or voided reaction, but has not essentially altered stereochemistry.

Phenolic compounds (42.8, 42.9, 42.12, 42.13, 45.8, 45.9, 45.12 and 45.13) were obtained by treatment of the corresponding methyl ethers with boiling 48 per cent hydrobromic $\operatorname{acid}^{(20.25,26)}$. There was no inversion of the hydroxyl or skeletal rearrangement as shown by diazomethane conversion of the phenols to the original methyl ethers.

Stereoselectivity of addition of platinum-oxide-catalyzed hydrogen has been observed also with 2'-methoxy-2,5-dimethyl-9-methylene-6,7-benzomorphan (47) obtained from the methyl carbinol (42.7) and thionyl chloride.



As the free base or hydrochloride salt in alcohol, this 9-methylene compound received hydrogen from the top side of the molecule giving α -2'-methoxy-2,5,9-trimethyl-6,7-benzomorphan (49) in good yield. In the presence of excess hydrochloric or perchloric acid (presumably to keep the nitrogen positive), on the other hand, the direction of addition was reversed and β -2'methoxy-2,5,9-trimethyl-6,7-benzomorphan (48) was obtained in 70 per cent yield. *O*-Demethylation of (49) and (48) to (34.1) and (35.1) respectively proved their identity⁽²⁷⁾.

4. N-SUBSTITUTED (OTHER THAN METHYL)-6,7-BENZOMORPHANS

As implied earlier, it had been the feeling that substitution of any group for the N-methyl of morphine and similar entities would have a detrimental effect on analgesic activity. However, in 1956 it was reported that replacement of methyl by phenethyl in the morphine molecule resulted in an eightfold increase in potency⁽²⁸⁾. A short time later this and similar modifications were reported for the morphinans^(29,30) and 4-phenylpiperidines^(31,32). In many instances the increase in potency was dramatic. Consequently a fairly representative group of N-substituted 6,7-benzomorphans have been synthesized. The most interesting of this group have proved to be N-phenethyl derivatives initially synthesized from parent N-methyl compounds as shown in Fig. 7 for α -2'-hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan (phenazocine) (54.3)⁽³³⁾. In this route, α -2'-acetoxy or methoxy-2,5,9-trimethyl-6,7-benzomorphan (50.1) or (50.2) was converted to the secondary amine (51.3) or (51.2) in two steps (cyanogen bromide followed by acid hydrolysis)^(33,34). Phenylacetylation of (51) with phenylacetyl chloride in the presence of aqueous methanolic potassium carbonate produced the amide (53) which can be reduced to the (54.2) or (54.3) with ethereal lithium aluminum hydride. Conversion of (54.2) to (54.3) was affected with boiling 48 per cent hydrobromic acid⁽³³⁾.

Similarly, the following 6,7-benzomorphans have been prepared: 5-methyl-2-phenethyl⁽³⁴⁾; 2'-hydroxy-5-methyl-2-phenethyl⁽⁸⁾; 5-ethyl-2'-hydroxy-2-phenethyl⁽¹⁰⁾; α -2',9-dihydroxy-5,9-dimethyl-2-phenethyl⁽²⁰⁾; α -5,9-diethyl-2'-hydroxy-2-phenethyl⁽¹⁵⁾; α -2-ethyl-2'-hydroxy-5,9-dimethyl⁽³⁵⁾; α -2'-hydroxy-5,9-dimethyl⁽³⁵⁾; α -2'-hydroxy-5,9-dime



 α -2-amyl-2'-hydroxy-5,9-dimethyl⁽³⁵⁾. Alternatively, 2'-hydroxy-5-methyl-2-phenethyl-6,7-benzomorphan^(8,†), 5-ethyl-2'-hydroxy-2-phenethyl-6,7-benzomorphan⁽¹⁰⁾ and (54.3)^(34,†) have been prepared from appropriate 1phenethylpyridinium bromides or iodides by the general methods outlined in Fig. 3, 4 and 5. Finally, 5,9-dimethyl-2-(3-phenyl-3-oxopropyl)-6,7-benzomorphan (52.4) and the 2'-hydroxy congener (52.3) were obtained from (51.4) and (51.3) respectively, via the Mannich reaction using formaldehyde and acetophenone⁽³⁶⁾. Many other *N*-substituted 6,7-benzomorphans have been synthesized in other laboratories. They are tabulated in the pharmacological section.

5. Optically active 5,9-dialkyl-6,7-benzomorphans – absolute configuration

It has been stated in Part IIA (p. 26) and in Section 2 of Part IIB (p. 119) that 3-hydroxy-N-methylmorphinan has three asymmetric carbon atoms (at 9, 13 and 14). However, since the iminoethano system is geometrically constrained to a *cis*-fusion, only two (racemic) diastereoisomers are possible. Of these, (\pm) -3-hydroxy-N-methyl-morphinan has been shown to conform to structure (2), (*cis*-fusion of rings B and C), while the second racemate may be represented by stereostructure (55), (\pm) -3-hydroxy-N-methylisomorphinan, with a *trans*-fusion of rings B and C⁽³⁷⁾. Similar considerations apply to the 5,9-di-

† E.L. MAY and J.H. AGRR (unpublished).

alkyl-6,7-benzomorphans in which it has been shown that the 5,9-dialkyl groups (attached to ring B) may be in either *cis* (predominant, α -isomers, (56)) or *trans*- (lesser, β -isomers, (57)) juxtaposition for the hydroaromatic ring B. Thus (56) corresponds to (2) and (57) to (55). It is also well known



(Part IIA) that nearly all of the analgesic activity of (2) and (55) is due in each instance to the *laevo*-antipode which in the case of (2) conforms to the absolute configuration of *(laevo)* morphine at the three common asymmetric centres (see Part IIA, p.26). Optical resolution of the α - and β -2'-hydroxy-2,5,9-trimethyl-6,7-benzomorphans (56, 57), the 5,9-dimethyl groups representing vestiges of ring C of the morphinans, has revealed an analogous relationship. The *dextro* isomers of (56) and (57) were not only substantially inactive but were also more toxic than the *laevo*-counterparts.

Resolution was effected with (+)-3-bromo-8-camphorsulfonic acid⁽³³⁾; the resultant diastereoisomeric salts could be easily separated in aqueous medium. The antipodes of the α -series (56) were then converted to the *N*-phenethyl derivatives (58.3)⁽³³⁾ as outlined in Fig.7 for the racemates. In



0.1 R==MeO, R₁==Me 0.2 R==MeO, R₁==CH₂CH₂Ph 0.3 R==HO, R₁==CH₂CH₂Ph

addition, antipodes corresponding to (58.1) and (58.2) have been prepared and characterized.[†]

In view of the fact that the analgesic activity of (56) does reside in the *laevo*isomer, and as it has been shown by the method of stereoselective adsor-

† E.L. MAY (unpublished).

bents⁽³⁸⁾ that ((-)-56) is configurationally related to (-)-3-hydroxy-*N*-methyl-morphinan (Levorphanol) and morphine, the (+)-isomer to (+)-3-hydroxy-*N*-methyl-morphinan (Dextrorphan), the (56) antipodes and related compounds may be represented by stereostructures (59) and (60).



Similarly ((-)-57) and ((+)-57) can probably be represented by (61) and (62).



6. MISCELLANEOUS 6,7-BENZOMORPHANS

(a) 8-Acetoxy and 8-hydroxy-2,5-dimethyl-6,7-benzomorphans



In initial attempts to convert 2,5-dimethyl-8-oxo-6,7-benzomorphan (63) to 2,5-dimethyl-6,7-benzomorphan (9) (Fig.2), platinum-oxide catalyzed hydrogen was used. Instead of complete hydrogenolysis, there was absorption of only one molar equivalent of hydrogen and carbinol (64) was obtained⁽⁵⁾. The stereochemistry of (64) at carbon 8 has not been determined but reasoning by analogy from the 9-oxo series^(19,25), the hydroxyl is presumed to be quasi-equatorially oriented (toward nitrogen). Acetic anhydride and (64) produced 8-acetoxy-2,5-dimethyl-6,7-benzomorphan (65)⁽⁵⁾.

(b) 9-Carbethoxy-2-methyl-6,7-benzomorphan and derivatives

If one replaces the 5-methyl substituent of 2,5-dimethyl-6,7-benzomorphan (9) with carbethoxy, a structure (68) is obtained which is in essence a hybrid of this benzomorphan and the well-known analgesic meperidine (4-carbethoxy-

1-methyl-4-phenylpiperidine) (71). Compound (71) was synthesized from phenylacetonitrile by a method closely approximating that used for (9) (Fig.2) as outlined in Fig.8⁽³⁹⁾. The reactions were all relatively straight-



forward and good yields were obtained. WOLFF-KISHNER conditions (HUANG-MINLON modification) for cyano ketone (66) effected both hydrogenolysis of the oxo group and hydrolysis of the cyano group. The resultant (67) could be esterified directly with ethanolic hydrogen chloride or indirectly via the acid chloride (70). The latter with dimethylamine yielded amide (69) which was reduced with lithium aluminum hydride to the aminomethyl compound (72).

(c) Open nitrogen compounds

In the course of degradative investigations on the 6,7-benzomorphans for confirmation of structure, intermediates were obtained in which the heterocyclic ring is cleaved between carbon 1 and nitrogen. These intermediates, tetrahydronaphthalenes, were prepared by the general scheme shown below (see references 5, 10, 11, 13, 14, 15 and 16) in Fig.9.

As would be expected the Hofmann elimination reaction of methiodides (73) occurs with ease as does the hydrogenation of (74). In one instance a phenolic compound (75.6) was prepared by treatment of (75.5) with boiling 48 per cent hydrobromic acid⁽¹⁴⁾.



Fig. 9

TABLE XIX. 1. 5-ALKYL (OR CARBOXYL)-2(N)-METHYL-6,7-BENZOMORPHANS

No.	ъ	ъ	Salt	ED	50 T	LD50†	0(7	
and Ref.	ef. R R_1	K ₁	San	subcut.	oral	subcut.	70 Base	
9(5)	н	Me	HCl	22.1	42.1	148	84.6	
10 ^(8,9)	HO	Me	HCl	10.4		175	85.6	
19.8 ⁽¹⁰⁾	HO	Et	HCl	2.3	11.2	171	86.4	
19.10 ⁽¹¹⁾	HO	Pr	HCl	2.1	14.8	130	87.0	
68 ⁽³⁹⁾	H	CO ₂ Et	HCl	10.1	43.8	141	82.8	
69 ⁽³⁹⁾	H	$CONMe_2$	HCl	18.3	33.8	(1)	84.0	
72 ⁽³⁹⁾	H	CH_2NMe_2	Di-HBr	None		(2)	60.1	
				to 100				

 \dagger mg/kg of substance as supplied, salt or base. See text for method of calculation. Same for Tables XX-XXIX.

- (1) None died at 100 mg/kg.
- (2) None died at 400 mg/kg.

TABLE XX. 2. 5,9-DIALKYL- $2(N)$ -methyl- $6,7$ -benzomorphans (a)	α-Series
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)/ R	R ₁			
No. and Ref.	Ъ	ъ	ъ	Salt	ED	50†	LD ₅₀ † subcut.	% Base
	R	к 1	K ₂		subcut.	oral		
29.1 ⁽⁹⁾	н	Me	Me	HCI	27.3	_	155	85.5
29.4*	н	Et	Et	HCI	5.0	36.7	83	87.0
29.3(11)	HO	Me	Me	HCI	3.0	23.9	175	80.9
29.2 ⁽¹⁴⁾	MeO	Me	Me	HBr	9.8	21.7	<u> </u>	75-2
50.1(17)	AcO	Me	Me	HCl	1.17	3.3	(1)	87.2
34.5(11,16)	HO	Et	Me	HCl	4.9	31.7	309	87.0
34.4 ^(11,16)	HO	Me	Et	HCl	1.5	14.8	134	87.0
34.2(15)	HO	Et	Et	HCl	4.2	I	423	87.7
34.7 =	AcO	Et	Et	HCl	3.0	28.9	252	89.2
34.6 ⁽¹¹⁾	HO	Pr	Me	HBr	2.9	72.1	(2)	76-2
34.3(11)	но	Pr	Pr	HCI	71.2	-	(3)	88.3

† See Table XIX.

⁺ A.E. JACOBSON and E.L. MAY, J. Med. Chem., 7, 409 (1964).

(1) Ten of 20 died at 200; three of 9 died at 300 mg/kg; $LD_{50} > 300$.

- (2) One of 10 died at 200, three of 9 died at 300 mg/kg; $LD_{50} > 300$.
- (3) One of 10 died at 400 mg/kg.

|--|



No. and Ref.	R	R ₁	R ₂	Salt	ED	50†	LD ₅₀ † subcut.	% Base
					subcut.	oral		
35.6 ⁽⁴⁰⁾	н	Me	Me	HBr	8.9	37.1	178	72.7
35.7 +	H	Et	Et	HBr	4.2	38.6	(1)	87.0
35.1(11,14)	HO	Me	Me	HCl	0.44	8.2	67	80-9
35.5(11,16)	HO	Et	Me	HCl	0.07	1.1	60.15	87.0
35.4(11,16)	HO	Me	Et	HCl	0.47	17.2	85.0	87.0
35.2(15)	HO	Et	Et	HCl	0.28	6.5	116	87•5
35.3(11)	но	Pr	Pr	HCl	0.87	-	62	88.8

† See Table XIX.

⁺ A.E. JACOBSON and E.L. MAY, J. Med. Chem., 7, 409 (1964).

(1) Ten of 10 died at 80 mg/kg, one of 10 at 60 mg/kg, and six of 10 at 120 mg/kg; LD_{50} ca. 80 mg/kg.

TABLE AATT. 5. 9-FIYDRUXY-2(1) J-METHYL-0, 7-BENZUMURPHANS (a) a-SERIE
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No. and Ref.		п	ъ	Salt	ED	50†	LD ₅₀ † subcut.	% Base
	ĸ	к ₁	К ₂		subcut.	oral		
42.4 ⁽¹⁹⁾	н	Me	н	HBr	63.8		(1)	73.2
42.5(19)	H	Me	Me	HBr	43.7		(1)	74.1
42.8(19)	HO	Me	Н	HBr	79.9			74.3
42.9 ⁽¹⁹⁾	HO	Me	Me	HBr	6.9			75.3
42.6 ⁽¹⁹⁾	MeO	Me	н	HBr	>100.0*		(2)	75.4
42.7(19)	MeO	Me	Me	HCl	19.7	13.5	373	82.7
42.12(26)	но	Et	Н	HCl	I	l	(3)	84.5
42.10(26)	MeO	Et	н	HCl	67.4		(4)	82.7
42.13(26)	но	Et	Me	Base	6.7	55.3	(5)	100.0
42.11(26)	MeO	Et	Me	HCl	13.8	43·0		83.6

† See Table XIX.

⁺ Five of 10 show some effect at 100 mg/kg but no effect at lower doses.

(1) Two of 10 died at 400 mg/kg.

(2) None died at 200 mg/kg.

(3) Three of 10 died at 400, none at 200 mg/kg.

(4) Eight of 10 died at 400, none at 200 mg/kg; LD₅₀ ca. 400 mg/kg.

(5) None of 10 died at 300 mg/kg.

TABLE XXIII. 3.	9-Hydroxy-20	(N)-methyl-	5,7-BENZOMORPHANS	(b)	β -Series
				· ·	

			f		R ₁			
No. and Dof		n	R ₂	Salt	ED ₅₀ †		LD ₅₀ †	0/ D
No. and Ref.	ĸ	K1			subcut.	oral	subcut.	% Base
45.5 ⁽¹⁹⁾	н	Me	Me	HCl	112-1		_	83.6
45.8 ⁽¹⁹⁾	но	Me	Н	HBr	I#		(1)	74.3
45.6 ⁽¹⁹⁾	MeO	Me	н	HBr	47.3		(2)	75.4
45.9 ⁽¹⁹⁾	HO	Me	Me	HBr	6.0		55	76.3
45.7 ⁽¹⁹⁾	MeO	Me	Me	HBr	I 20		63	75.8
45.12 ⁽²⁶⁾	HO	Et	н	HC1	12.2		(3)	87.1
45.13(26)	HO	Et	Me	HBr	1.7		74	74.5
45.14(26)	MeO	Me	Et	HCI	8.4		(4)	88.2

R₂ R₁ R₁ NCH₃

† See Table XIX.

⁺ Only four of 10 affected at 100 mg/kg; no effect at lower doses.

(1) One of 10 died at 200 mg/kg.

(2) Four of 10 died at 100 mg/kg.

(3) Three of 10 died at 400, none at 200 mg/kg.

(4) Three of 16 died at 50 mg/kg while testing for analgesia.

TABLE XXIV. 9-ACETOXY-2(N)-METHYL-6,7-BENZOMORPHANS &-SERIES



No. and Def	ъ	Ъ	D	Salt	ED	50†	LD₅0† subcut.	% Base
No. allu Kel.	к 	к1	К <u>2</u>	San	sub :ut.	oral		
42.22 ⁽¹⁹⁾	н	Me	н	HBr	29.0		367	76.2
42.15(19)	AcO	Me	H	HBr	0.2	40.5	(1)	79.7
42·16 ⁽¹⁹⁾	AcO	Me	Me	HBr	1.1	22.5	-	80.4
42.17 ⁽²⁶⁾	MeO	Et	н	HCl	22.6		197	89.0
42.21(26)	AcO	Et	Н	HCI	2.2	10.6	262	90.0
42.19 ⁽²⁶⁾	HO	Et	Me	HCI	1.13	I‡	(2)	89.3
42.18 ⁽²⁶⁾	MeO	Et	Me	HCl	14.8		(3)	89.5
42.20 ⁽²⁶⁾	AcO	Et	Me	HCI	1.15	72.3	(3)	90•4

† See Table XIX.

+ Only four of 10 affected at 100.

(1) One of 10 died at 200 mg/kg.

(1) Five of 10 died at 400, one of 10 at 200 mg/kg; LD_{50} ca. 400 mg/kg. (3) Three of 10 died at 400 mg/kg, none at lower doses; $LD_{50} > 400$ mg/kg.

TABLE XXV. 4. N-SUBSTITUTED (OTHER THAN METHYL)-6,7-BENZOMORPHANS (a) 5-Alkyl and α -5,9-dialkyl-2(N)-alkyl or aralkyl-6,7-BENZOMORPHANS



р	Ъ	R. R.		Salt	ED50†		LD50 [†]	% Base
K	K K ₁	К ₂	К3	San	subcut.	oral	subcut.	/0 Base
H HO HO MeO	Me Me Et Me Me	H H Me Me	CH_2CH_2Ph CH_2CH_2Ph CH_2CH_2Ph CH_2CH_2Ph CH_2CH_2Ph CH_2CH_2Ph CH_2CH_2Ph	HCl HBr HCl HBr HBr	35-9 0-48 0-16 0-25 6-5 0-19	 7·9 6·0 6·4 10·6 6·1	>400 55 88 332 	88·9 79·2 88·4 79·9 80·5 81·3
HO HO H HO MeO HO	Me Et Pr Me Me Me	Et Me Me Me Me Me	$CH_{2}CH_{2}Ph$ $CH_{2}CH_{2}Ph$ $CH_{2}CH_{2}CPh$ $CH_{2}CH_{2}COPh$ $CH_{2}CH_{2}COPh$ $CH_{2}COPh$ $CH_{2}CH_{2}CH_{2}Ph$	HBr HCl HCl Base HCl Base	2·1 0·92 8·7 2·3 42·9 13·6	I 38·1 I 30·2 	$ \begin{array}{c} 109\\ 292\\ (1)\\ (2)\\ 83\\ (3)\\ - \end{array} $	81-3 90-3 91-2 100-0 89-8 100-0
НО	Me	Me	CH ₂ CH ₂ -NH ₂	Base	0.11	10.7	125	100-0
НО	Me	Me	CH ₂ CH ₂ -OMe	HBr	0.32	18.9	(4)	81.3
НО	Me	Me	CH2CH2OH	HBr	0·2 (rat)		-	81·2
	R H HO HO HO HO HO HO HO HO HO	RR1H HO HO HO AcO HO HO HO HO HO HO HO HO HO HO HO HO HO Me Me Mo	RR1R2HMeHHOMeHHOEtHHOMeMeMeOMeMeAcOMeMeHOEtEtHOPrMeHOMeMeHOMeMeHOMeMeHOMeMeHOMeMeHOMeMeHOMeMeHOMeMeHOMeMe	R R_1 R_2 R_3 HMeH CH_2CH_2Ph HOMeH CH_2CH_2Ph HOEtH CH_2CH_2Ph HOMeMe CH_2CH_2Ph HOMeMe CH_2CH_2Ph AcOMeMe CH_2CH_2Ph HOEtEt CH_2CH_2Ph HOEtEt CH_2CH_2Ph HOMeMe CH_2CH_2CPh HOMeMe CH_2CH_2COPh HOMeMe CH_2CH_2COPh HOMeMe $CH_2CH_2CH_2Ph$	R R_1 R_2 R_3 SaltHMeH CH_2CH_2Ph HClHOMeH CH_2CH_2Ph HBrHOEtH CH_2CH_2Ph HBrHOMeMe CH_2CH_2Ph HBrHOMeMe CH_2CH_2Ph HBrHOMeMe CH_2CH_2Ph HBrHOMeMe CH_2CH_2Ph HBrHOEtEt CH_2CH_2Ph HBrHOPrMe CH_2CH_2CPh HClHOMeMe CH_2CH_2COPh BaseMeOMeMe $CH_2CH_2CH_2Ph$ BaseHOMeMe $CH_2CH_2CH_2Ph$ BaseHOMeMe CH_2CH_2 $-NH_2$ BaseHOMeMe CH_2CH_2 $-OMe$ HBrHOMeMe CH_2CH_2 $-OMe$ HBrHOMeMe CH_2CH_2 $-OH$ HBr	R R_1 R_2 R_3 SaltED:HMeH CH_2CH_2Ph HCl35·9HOMeH CH_2CH_2Ph HBr0·48HOEtH CH_2CH_2Ph HBr0·16HOMeMe CH_2CH_2Ph HBr0·25MeOMeMe CH_2CH_2Ph HBr0·19HOEtEt CH_2CH_2Ph HBr0·19HOEtEt CH_2CH_2Ph HBr0·19HOEtEt CH_2CH_2Ph HBr0·19HOHMe CH_2CH_2Ph HBr0·21HOMeMe CH_2CH_2CPh HCl8·7HOMeMe CH_2CH_2COPh Base2·3MeOMeMe CH_2CH_2CPh HCl42·9HOMeMe CH_2CH_2 -NH2Base0·11HOMeMe CH_2CH_2 -NH2Base0·11HOMeMe CH_2CH_2 -OMeHBr0·32HOMeMe CH_2CH_2 -OHHBr0·2 (rat)	R R1 R2 R3 Salt ED50 [†] H Me H CH2CH2Ph HCl 35·9 HO Me H CH2CH2Ph HBr 0·48 79 HO Et H CH2CH2Ph HBr 0·48 79 HO Et H CH2CH2Ph HBr 0·48 79 HO Me Me CH2CH2Ph HBr 0·48 79 HO Me Me CH2CH2Ph HBr 0·16 6·0 HO Me Me CH2CH2Ph HBr 0·19 6·1 HO Et Et CH2CH2Ph HBr 0·19 6·1 HO Pr Me CH2CH2Ph HBr 0·19 6·1 HO Me Me CH2CH2COPh HBr 2·1 I HO Me Me CH2CH2COPh HCI 8·7 I HO Me	$\begin{array}{c c c c c c c c c c c c c c c c c c c $

TABLE XXV—continued

No. and Def	П	ъ	рр		Co.1t	ED ^{†50}		LD50 [†]	% Base 100-0 85-7 80-8 75-2 87-7 77-1 88-7 92-8 100-0 87-7 77,6 100-0
No. allu Kel.	K	к1	R ₂	К3	San	subcut.	oral	subcut.	% Dase
52.10 ⁽⁴¹⁾	НО	Me	Ме	CH_2CH_2	Base	0.055	5.8	88	100-0
52.11 ^(35.41) 29 [,] 3 ^(7,13)	HO HO	Me Me	Me Me	H Me	HCl HCl	I 3·0	23.9	84 175	85·7 80·8
$52.12^{(35)}$ $52.13^{(35)}$	HO HO	Me Me	Me Me	Et Pr	HBr HCl	I I		(5) 137	75·2 87•7
52.14 ⁽³⁵⁾ 52.15 ⁽³⁵⁾	HO	Me	Me Me	Bu	HBr HCl	I 2·2	 88·7	341 (6)	77·1 88·7
52.16 ⁽⁴¹⁾	0 ₂ NC00	Me	Me	CH ₂ CH ₂ Ph	HCI	0.41	14·6	-	92.8
52.17 ⁽⁴¹⁾	COO N	Ме	Me	CH ₂ CH ₂ Ph [≠]	Base	0.17	13.5	393	100.0
52.18 ^(41,42) ††	HO HO	Me Me	Me Me	$CH_{2}CH = CH_{2}$ $CH_{2}CH = CH_{2}$	HCl Allobromide	I I		(7)	87·7 77,6
52.19(42)	НО	Me	Me	CH ₂	Base	23.1		(8)	100-0
52.20 ⁽⁴²⁾ 52.21 ⁽⁴²⁾	HO HO	Me Et	Me Me	$CH_{2}CH=CMe_{2}$ $CH_{2}CH=CMe_{2}$	Base Base	I 15.9		(9) (10)	100-0 100-0

† See Table XIX.

- + Laevo isomer
- †† Supplied by C.H.BOEHRINGER.
- (#) J.H. AGER, (unpublished).
- (1) None of 10 died at 400 mg/kg.
- (2) One of 10 died at 400 mg/kg.
- (3) None of 10 died at 400 mg/kg.

(4) Three of 10 died at 450 mg/kg.

(5) Two of 10 died at 100 mg/kg during analgesic testing.

(6) Ten of 10 died at 400, none of 10 at 200 mg/kg; $LD_{50} = 400$ mg/kg or less.

- (7) Four of 8 died at 50 mg/kg; $LD_{50} = ca. 50 \text{ mg/kg}.$
- (8) One of 10 died at 300 mg/kg.

(9) Eight of 10 died at 400 mg/kg; $LD_{50} = ca. 400 \text{ mg/kg}.$

(10) Two of 10 died at 300 mg/kg.

R R NCH ₂ CH ₂ Ph CH ₃									
No. and Ref.	R	R ₁	Salt	ED ₂ subcut.	so† oral	LD ₅₀ † subcut.	% Base		
54.9 ^(19,25) 54.10 ^(19,25) 54.11 ^(19,20)	HO MeO HO	H H Me	HCl HBr HBr	0.62 22.2 7.5	31·3 I	(1) (2) 209	84·5 80·7 80·6		

TABLE XXVI. (b) α -9-Hydroxy-2(N)-phenethyl-6,7-benzomorphans

† See Table XIX.

(1) Four of 10 died at 100, two of 10 at 60 mg/kg.

(2) Two of 10 died at 400 mg/kg.

TABLE XXVII.	5.	OPTICALLY	ACTIVE 5,9	-dimethyl-6,	7-benzomorphans	(a)	α-Series
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			Ŕ	0.1.3				
No. and Def	Leomor	ъ	ъ	Salt	ED	50 T	LD 50 1	0/ Daga
No. and Ker.	Isomer	ĸ	К1	San	subcut.	oral	subcut.	7_0 base
59 ⁽³³⁾	laevo	но	Me	HBr	1.69	14.1	(1)	74.1
60 ⁽³³⁾	dextro	HO	Me	HBr	I		(2)	74.1
59.1*	laevo	MeO	Me	HBr	8.7	17.9	175	75·2
60.1 <i>‡</i>	dextro	MeO	Me	HBr	I		176	75-2
54.12 ⁽³³⁾	laevo	HO	CH ₂ CH ₂ Ph	HBr	0.11	3.9	147	79.9
54.13 ⁽³³⁾	dextro	HO	CH ₂ CH ₂ Ph	HBr	6.6	12.9	201	79•9
54.14 [‡]	laevo	MeO	CH ₂ CH ₂ Ph	HBr	1.83		(3)	80.5
54.15 [‡]	dextro	MeO	CH₄CH₂Ph	HBr	I	-	-	80•5

(b) β -Series



61 ⁽¹⁷⁾ 62 ⁽¹⁷⁾	laevo dextro	_		HBr HBr	0·39 15·75	6.6	118	
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† See Table XIX.

+ Unpublished data.

(1) None died at 400 mg/kg.

- (2) Convulsant at 20 mg/kg; all recovered.
- (3) Three of 10 died at 500 mg/kg.

TABLE XXVIII. 6. MISCELLANEOUS DERIVATIVES (a) 2,5-DIMETHYL-6,7-BENZOMORPHANS WITH SUBSTITUTIONS AT CARBON-8



No. and Dof	Ъ	Salt	EI	LD ₅₀	
No. allu Rei.	ĸ	San	subcut.	oral	subcut.
63 ⁽⁵⁾ 64 ⁽⁵⁾ 65 ⁽⁵⁾	=0 OH OAc	HCl HCl HCl	I 29·3 32·2	 29·3	690 323 289

TABLE XXIX. (b) 1-(2-DIMETHYLAMINOETHYL)-1,2,3,4-TETRAHYDRONAPHTHALENES



No. and Def		п		Calt.	ED	50†	LD ₅₀ †	
No. and Kei.	ĸ	к ₁	R ₂	San	subcut.	oral	subcut.	
75.1 ⁽⁵⁾	н	Me	н	HCl	24.9	-	362	
75.2 ⁽¹³⁾	н	Me	Me	HCl	41.1		411	
75.8 ⁽¹⁶⁾	MeO	Et	Me	HCl	I			
75.4(11)	MeO	Pr	н	HCl	I	<u> </u>	(1)	
75.5(14)	MeO	Me	Me	HBr	27.1		649	
75.6(14)	но	Me	Me	HCl	I	→	>600	
75.7 ⁽¹⁶⁾	MeO	Me	Ει	HCI	25.7	I	(3)	
75.9 ⁽¹¹⁾	MeO	Pr	Pr	HCI	I		(4)	

† See Table XIX.

(1) One of 10 died at 200 mg/kg.

(2) One of 5 died at 600 mg/kg.

(3) Ten of 10 died at 400, none at 300 mg/kg; $LD_{50} = ca. 400 \text{ mg/kg}$.

(4) None died at 200 mg_l/kg .

CHAPTER IV

Pharmacology of the 6,7-Benzomorphans

1. Analgesic and toxic effects in animals

The same techniques have been employed † for the study of all compounds for analgesia and toxicity. For the former the hot plate method, as modified and developed by EDDY and LEIMBACH⁽⁴³⁾, has been used with calculation of ED_{50} 's by probit analysis. All compounds were tested by subcutaneous administration in mice and most of the more active ones by oral administration as well. The solubility of the benzomorphans is low generally and in many instances a substance was dissolved in a small amount of propylene glycol with subsequent dilution to make the propylene glycol concentration not more than 25 per cent. If the material was supplied as a base, solution was effected by the addition first of the approximately calculated amount of NHCl. The final concentration of active ingredient was always such that the dose administered was 0.01 mg/g mouse weight. So far as quantity of material available permitted, toxicity for mice by subcutaneous administration, 10 or 20 animals per dose, was determined and an LD_{50} calculated by probit analysis. In the tables all doses are in mg/kg of compound as supplied, but, since the nature of a compound as base or salt and the per cent of base are also given, the data may be recalculated in terms of base. Unless otherwise indicated all compounds tested were the racemates.

Identification of compounds is by formula number and their arrangement in Tables XIX-XXIX parallels the description of chemical preparation already given. However, it seems more appropriate to discuss structure activity relationships by pairs of compounds differing from each other in one respect only, considering in succession the results of changes made at positions 2', 5, 9 and 2 of the benzomorphan molecule. To accomplish this some rearrangement of the data have been made. The effect of isomeric configuration and activity by oral vs. subcutaneous administration will also be described.

(a) Effect of the substituent at 2' in the unsaturated ring of 6,7-benzomorphans (see Table XXX)

In the main the changes in analgesic activity parallel those seen with similar modifications of the substituent at the corresponding position 3 in the mor-

† Except for a few compounds made in other laboratories and not seen by us.

phine and morphinan series – increase in activity by the introduction of a phenolic hydroxyl, reduction of activity by the change from OH to OCH₃, and restoration of analgesic effect by acetylation, generally beyond that of the compound with a free hydroxyl. There are some exceptions. In the group, (42.4, 42.8, 42.6), the change from H to OH at 2' did not increase analgesic activity, but the further change to OCH₃ reduced it. In the group, (75.2, 75.6, 75.5), in which the nitrogen ring was not closed, the compound with the free hydroxyl was the least active and the methoxyl derivative was most active with respect to analgesia.

Three other compounds should be mentioned here, (52.22) which has methoxy methoxy, (52.16) which has *p*-nitrobenzoyl, and (52.17) which has nicotinyl at position 2'. Each is an active analgesic but a little less so than the analog with a free hydroxyl at position 2'.

Toxicity figures are scattered for this group but no consistent trend is apparent which might be related to the substituent at position 2'.

(b) Compounds with substituents at positions 2 and 5 but H only at 9 of 6,7-benzomorphans

There are seven related compounds in this category (Table XVIII) falling into two groups, – one with H only, the other with OH at 2'. In neither group was CH_3 at 5 optimal for analgesic effectiveness. For the substituents tested the decreasing order of analgesic potency was $COOC_2H_5 > CON(CH_3)_2$ $> CH_3 > CH_2N(CH_3)_2$ with H at 2'; C_3H_7 and C_2H_5 approximately equal $> CH_3$ with OH at 2'.

(c) The effect of a substituent at position 9 of 6,7-benzomorphans

The appropriate compounds have been rearranged into groups (Table XXI) with the basic structure within each group the same and modifications only in the substituent at position 9. The nature of the added radical or radicals is important but also important are their orientation and the presence or absence of the hydroxyl at 2'. With one exception, (35.6), less analgesic action was demonstrated with OH, CH₃ or OCOCH₃ at 9 if there was no hydroxyl at 2', the reduction in activity being greatest with OH. On the other hand with CH₃ or C₂H₅ at 9 analgesic activity was increased if there was a free OH at 2', but dihydroxy compounds with the second OH at 9 again were less effective than compound No.10 which was 2'-OH with H at 9. Compounds with alkyl substituents at 9 oriented away from nitrogen (α) were less effective generally than those in which the same substituent was oriented toward the N-ring (β). (35.5) falls just short of being the most potent analgesic which has been synthesized to date in the benzomorphan series. It is 30 times more effective than morphine and to our knowledge, the most active analgesic known of morphine-like structure with methyl on nitrogen.

SA. 10

In the four comparisons available OH or CH_3 at 9 in α -position relative to N seemed to reduce toxicity; the effect of other alkyl groups at 9 was not consistent.

(d) The effect of modifying the substituent at 2', N-alkyl or N-aralkyl derivatives of 6,7-benzomorphan

It was long the consensus that N-CH₃ was the optimal grouping for analgesic activity in morphine and related compounds. No doubt this came about because N-ethylnormorphine was a poorer analgesic than morphine and N-allyl- and N-propylnormorphine were not only practically devoid of analgesic action in animals but exhibited antagonistic properties towards analgesic and other morphine-like effects. However, WINTER and his associates⁽⁴⁴⁾, explored extensively the effect of various substituents on the nitrogen of morphine with respect to analgesic and antagonistic effects. They found, as had others, that N-cthylnormorphine had only one-tenth the analgesic effectiveness of morphine: that N-allyl- and N-propylnormorphine had little or no analgesic effect and were antagonistic, that N-butylnormorphine was weak in both analgesic and antagonistic properties, but curiously, N-amylnormorphine was almost as good an analgesic as morphine itself. A little later EDDY et al.⁽⁴⁵⁾ reported that N-cthyl-3-hydroxymorphinan had very much less analgesic action than the N-methyl analog (Levorphanol) and the antagonistic potency of N-allyl-3-hydroxymorphinan (Levallorphan) is now well known. We have shown recently † that N-amyl-3-hydroxy-morphinan has an ED_{50} for analgesic action in mice practically identical with that for levorphanol. It is interesting, therefore, that in the benzomorphan series also (Table XVI) the sequence for changes in the alkyl substituent on nitrogen is the same – disappearance of effect with 2,3 or 4-carbon straight chain alkyl groups and reappearance of good analgesic effect when the substituent is anyl. The further parallelism of appearance of antagonistic properties with 3carbon alkyl groups has also been demonstrated. (See below.)

In their survey of the effect of substitution on nitrogen in the morphine series, WINTER *et al.*⁽⁴⁴⁾ also reported on the effect of the addition of various aralkyls. *N*-Phenacyl-, *N*-phenoxyethyl-, *N*-benzyl- and *N*-cyclohexylethyl-normorphine had less analgesic effect but *N*-phenethylnormorphine was six times more potent than morphine itself. Again, as reported by EDDY *et al.*⁽⁴⁵⁾ a parallelism in the analgesic activity of derivatives of this type carried over to the morphinan series. Scanning Table XXXII shows that in the benzomorphan series also a compound with an aralkyl on nitrogen may be a better analgesic than if the nitrogen substituent is alkyl (CH₃ or C₅H₁₁). (54.3) (phenethyl on N), (52.7) (*p*-aminophenethyl on N) and (52.8) (*p*-methoxyphenethyl on N) are seven to twenty times more potent as analgesics than (29.3) (CH₃ on N) and (52.10) (thienylethyl on N) is the most potent anal-

† Unpublished results.
gesic in the benzomorphan series which has been made. The *N*-thienylethyl derivative was one of the most potent in the morphinan series. (52.3) (3-oxo-3-phenylpropyl on N) was scarcely more effective and (52.6) (phenylpropyl on N) was definitely less effective than (29.3), which carries the parallelism with the morphinans a little further (see 45).

When phenethyl was substituted on nitrogen in place of methyl with the structure of the benzomorphan modified in other respects, analgesic activity was greater in the phenethyl derivative in 10 of the 12 comparisons (Table XVI), the range of increased activity spreading from 1.5 to 128 times. One exception was (52.4) in which there was no hydroxyl at the 2' position, of itself an adverse structural feature. The other exception was (54.11) in which a second OH was introduced in *cis*-position at carbon 9, further indicating probably the undesirability of an hydroxyl in that position.

In the series, (52.11-52.15), toxicity decreased with the length of the alkyl chain on N. Compounds with aralkyl on N were not consistently more or less toxic than those with alkyl on N. In *N*-phenethyl compounds, for example, a configuration which was almost always accompanied by increased analgesic activity, toxicity was sometimes greater, sometimes less than with the corresponding *N*-alkyl derivative.

(e) Configurational and optical isomerism in the benzomorphan series

The compounds having the alkyl group at position 9 oriented away from the nitrogen have been termed arbitrarily alpha, α , while those with the alkyl at 9 toward nitrogen are called beta β . Compare Tables XX and XXI for the α - and β -compounds with an alkyl group only at position 9, and Tables XXII and XXIII for α and β compounds in which there is also an hydroxyl at 9. In the former, with one exception, analgesic effectiveness is greater, in two instances very much greater for the β compounds. In the latter, however, the beta compounds were in only three cases more analgesic; in four others, the beta compounds were the less effective. In other words, the adverse effect of OH at 9 would seem to be generally more pronounced with an associated alkyl group *cis* to the plane of the molecule.

The few compounds which have been resolved into their *laevo*- and *dextro*components are listed in Table XXVII. Analgesic effect resides predominantly in the *laevo*-isomer. The *dextro*-isomer of phenazocine, (54.13), and the *dextro*-isomer of the β -N-methyl analogue of phenazocine, (62), are the only *dextro*-isomers which appear to possess significant analgesic activity. There is no indication that toxicity would be favorably influenced by resolution and use of the more active *laevo*-component.

Toxicity of the β -compounds was the same (two comparisons) or greater (six comparisons) than that of the α -isomers. However, analgesic activity was increased more than toxicity in the β -series, so that even in those pairs in which the toxicity of the isomers was the same, the ratio of analgesic to toxic properties was significantly greater for the β -series.

(f) Parenteral vs. oral effectiveness

Oral analgesic effectiveness was determined for about half of the compounds listed in Tables XIX-XXIX. With only two exceptions the oral dose was approximately two or more times the parenteral. When the subcutaneous ED_{50} was small (less than 1.0 mg/kg) the oral ED_{50} was 8-100 (average 41) times greater. When the subcutaneous ED_{50} was 2.0 mg/kg or more the oral ED_{50} was only exceptionally 8 or more times larger. There is, however, no indication of a structural relationship to this difference in ratios. The two exceptions in which the oral dose was not greater than the parenteral, were (42.7) (Table XXII and (65) (Table XXVIII). The pair are not closely related.

2. Studies of physical dependence capacity and chronic administration in monkeys

Unfortunately, limited supply of materials has permitted trial in the monkey of only about a third of the benzomorphans and for the same reason selection for such trial has not been wholly systematic. Data are available, however, on enough compounds to warrant some discussion.[†]

The technique for determination of physical dependence capacity in the monkey has been described in detail⁽⁴⁶⁾. The primary and principal objective is to ascertain whether or not a test drug is capable of suppression of all abstinence signs in the morphine-dependent monkey. This is based on the principle, demonstrated in animal and man, that any chemical substance capable of complete suppression of all of the specific signs of morphine abstinence is capable of creating physical dependence during chronic administration. Abstinence suppression ability is termed physical dependence capacity (PDC). It is characterized as *High*, when the experimental drug produces complete suppression of all abstinence signs with doses which reveal no other overt pharmacological effect; Intermediate, when complete suppression of all abstinence signs is obtainable, but only with doses which elicit other pharmacological actions, manifested by such signs as stupor, ataxia, tremor, etc.; Low, when some suppression of abstinence signs is induced, but attempts to produce more or complete suppression with larger doses is prevented by the intervention of toxic effects, such as coma, convulsions, etc.; None, when the drug fails to produce any specific suppression of the morphine abstinence signs. Non-specific depressants may obscure individual signs.

[†] We are indebted to Drs. Maurice H.Seevers and Gerald A. Deneau of the Department of Pharmacology of The University of Michigan, Ann Arbor, Mich., U.S.A. for permission to quote results obtained in the monkey, most of which have been reported in Addenda to the Minutes of the Committee on Drug Addiction and Narcotics of the National Academy of Sciences—National Research Council, U.S.A., for the years 1958–1962. Monkeys develop tolerance and physical dependence during chronic administration of morphine in a manner comparable to the development of these phenomena in man and the abrupt withdrawal of morphine or the administration of nalorphine to the monkey after physical dependence has developed results in characteristic symptomatology comparable to the abstinence syndrome in man.

For testing physical dependence capacity monkeys are maintained in a state of physical dependence by the subcutaneous administration of 3 mg/kg of morphine sulfate every 6 hr without interruption. The stabilization period is a minimum of 60 days. For testing, regular morphine injections are withheld for 12-14 hr until abstinence signs of intermediate intensity are present. If left untreated the abstinence signs increase progressively over the next several hours, but the administration of morphine or any drug with morphine-like physical dependence capacity results in a partial or complete suppression of the signs of abstincnce. A pre-selected quantity of the test drug, based generally on its analgesic potency, and 3 mg/kg of morphine sulfate are administered subcutaneously, each drug to two monkeys. The intensity of the abstinence signs is graded prior to and at intervals after administration until the monkeys have returned to the pre-injection level of excitability. Further testing is done with all drugs which are shown to have high or intermediate physical dependence capacity to extend the series of animals to confirm the estimate of physical dependence capacity and to determine the potency of the test drug relative to morphine. Physical dependence capacity and abstinence suppression potency are not synonymous and may not even parallel each other relative to morphine.

In the quantitative potency study five single-dose suppression treatments are each administered to five monkeys on a double blind basis in a Latin square pattern at weekly intervals. These are X (the dose of the test drug which in the initial test is approximately equipotent to 3 mg/kg of morphine), $\frac{1}{2}X$, 2X, and two controls, 3 mg/kg of morphine sulfate and a placebo (a saline injection). The results are plotted and from the peaks of the average time-effect curves which are obtained for each treatment a dose-effect curve is established. The potency of the test agent relative to morphine, (morphine equivalence; i.e. dose equivalent to 3 mg/kg of morphine in abstinence suppressant potency) is determined from this curve.

The observations on administration of benzomorphans to morphine-dependent monkeys are summarized in Tables XXX, XXXI and XXXII, and the results in the monkeys are compared with analgesic activity in Table XXXIII.

It is immediately apparent that the benzomorphans as a class have low physical dependence capacity, especially so relative to their analgesic effectiveness. The standard abstinence suppressing dose of morphine is only a little above its analgesic ED_{50} , 3.0 vs. 2.1 mg/kg. On the other hand, 19 of the benzomorphans had an ED_{50} for analgesia less than that for morphine, but only one had a morphine equivalence dose less than 3.0 mg; only three

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were rated high and only three others intermediate in PDC. There is a rough parallelism between analgesic activity and PDC in this group, but there are some notable exceptions. Most of the compounds which were weaker than morphine with respect to analgesia are in the group which had no physical dependence capacity, but in this same group there are three which had a greater analgesic effect than morphine. Also in the group rated low in PDC seven were more effective than morphine as analgesics and among these is the most potent analgesic yet encountered in the benzomorphan series.

The overall addictiveness of (54.3) (phenazocine) will be discussed later since it is one benzomorphan which has been studied extensively in man and is presently marketed. It and its *laevo*-isomer, (54.12), were rated high in PDC but whereas their ED_{50} 's were 0.25 and 0.11 mg/kg their morphine equivalent doses for abstinence suppression were 17.0 and 9.0 mg/kg respectively. Phenazocine was also administered chronically to monkeys. Animals which had not previously received drug were given phenazocine subcutaneously every 6 hr without interruption, 2 mg/kg the first week, 4 mg/kg the second week, 8 mg/kg the third week and 16 mg/kg thc fourth and fifth weeks. The animals were challenged with nalorphine, 2 mg/kg on the 28th day and abruptly withdrawn on the 35th day. The degree of abstinence precipitated by nalorphine and observed on withdrawal was of only intermediate intensity, definitely less than would be expected with similar administration and increase in dosage of morphine.

3. EFFECTS IN MAN, INCLUDING STUDIES OF TOLERANCE AND PHYSICAL DEPENDENCE

Initial studies of analgesic potency of (54.3) (\pm 2'-hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan, phenazocine[†], Prinadol[‡], Narphen[‡]) indicated an increase in effect over morphine in animals of nearly 10-fold. On the other hand, the compound proved to be a poor suppressant of morphine abstinence phenomena in the monkey, 17.0 mg/kg of the former being required to equal the effect of 3.0 mg/kg of the latter. Since low abstinence suppressant potency was believed to be indicative of reduced ability to produce physical dependence, these initial results suggested a significant separation of analgesic and addictive properties and encouraged three developments – a broad pharmacological examination to determine safety and the ability of the agent to produce various aspects of the morphine picture, the initiation of clinical trials, and investigation of the compound at the Addiction Research Center for a delineation of its morphine-like subjective, phys-

- † Generic and proposed International Nonproprietary Name.
- ⁺ Trade name, Smith, Kline & French, Philadelphia, Pa., U.S.A.
- # Trade name, Smith & Nephew, London, England.

ical dependence and tolerance developing properties in man. MAY and EDDY said in 1959, "Initial clinical experiments with this racemate, (54.3), show it to be a promising agent for the relief of both acute and chronic pain" (47).

ECKENHOFF⁽⁴⁸⁾ published the first report giving details of the use of the drug in patients, 150 in the immediate post-operative period. The indication was post-operative restlessness in 91 and acute post-operative pain in 59 patients. The doses used were 0.5, 1.0 and 1.5 mg, a few initially intravenously, but most intramuscularly. They were 95 per cent effective against postanesthetic restlessness with 68 per cent of the patients going back to sleep. The degree of effect ranged from 50 per cent for the 0.5 mg dose to 89 per cent for the 1.5 mg dose for acute post-operative pain with 37.5 per cent of the patients falling asleep. None of the patients experienced nausea or vomiting which could be attributed to the drug. While some evidence of an effect upon respiration and circulation was seen, this was less than had been cncountered with either morphine or pethidine under comparable conditions. ECKENHOFF also described the use of phenazocine in 10 cases of chronic pain and gave detailed case histories for four of them. In the cases cited, 1.5 to 3.0 mg of phenazocine intramuscularly gave better relief than previously used narcotics, pethidine 75-100 mg morphine 10 mg and dextromoramide. One patient withdrawn after three weeks showed no withdrawal signs. A second patient challenged with 5.0 mg of nalorphine after 37 days of phenazocine (2.5 mg every 4 hr during the day and 3.0 mg at night) responded in 30 min with profuse sweating, restlessness, nausea and mental confusion. A third patient, who was given 5.0 mg, of nalorphine after five weeks of phenazocine, noted only sleepiness. The phenazocine at a dose of 1.0 mg had given complete relief of 5-6 hr duration.

Shortly after ECKENHOFF's report three others on the clinical trial of phenazocine appeared (WALLENSTEIN *et al.*⁽⁴⁹⁾; SADOVE and SCHIFFRIN⁽⁵⁰⁾; and DEKORNFELD and LASAGNA⁽⁵¹⁾). The first was a cross-over double blind comparison of graded doses of phenazocine and morphine in patients with chronic pain due to advanced cancer. Each patient received 8 and 16 mg of morphine sulphate and either 1 and 2, 2 and 4, or 3 and 6 mg of phenazocine. In terms of peak and total analgesic effect phenazocine proved to be roughly three or four times as potent as morphine. The incidence of side effects of both drugs in these doses was small in these patients, with phenazocine showing a slight though not significant advantage. In a later report, these authors (HOUDE *et al.*⁽⁵²⁾) estimated the potency of phenazocine as $4\cdot3$ times that of morphine for peak and $3\cdot3$ times that of morphine for total analgesic effect. They said also that intramuscular doses were more than five times as effective as oral.

SADOVE and SCHIFFRIN⁽⁵⁰⁾ reported on 21 patients, selected from the recovery room population, who had pain severe enough to justify the use of a narcotic analgesic. They were followed for 120 min after intramuscular injection of the phenazocine dose of 2.0 mg. Satisfactory analgesia was attained in 17 patients, 81 per cent. Some respiratory depression was seen. Averaging the lowest minute volume observed for each patient after drug administration, the figure was 6.01 l., 62.7 per cent of the initial value.DEKORNFELD and LASAGNA⁽⁵¹⁾ observed their patients during the first

DEKORNFELD and LASAGNA⁽⁵¹⁾ observed their patients during the first 48 hr after surgery and alternated doses of 10 mg of morphine with doses of 0.5, (17 pt) 2.0 (19 pt) and 3.0 mg (22 pt) of phenazocine. The results were definitely inferior to those with morphine when 0.5 or 2.0 mg of phenazocine were employed. At the 3.0 mg level, however, the efficacy of phenazocine was essentially indistinguishable from that of the standard dose of morphine. It produced less sedation apparently, since patients had to be awakened for interview as to pain present at 42.4 per cent of observation times, whereas those receiving morphine had to be awakened 55.6 per cent of the time. Nausea and vomiting were observed twice after the 3.0 mg dose of phenazocine.

Meanwhile, WENDEL, SHEMANO and ROSS^(53,54) and TEDESCHI, TEDESCHI and FELLOWS⁽⁵⁵⁾ explored extensively the morphine-like pharmacological properties of phenazocine and a number of other investigations broadened our knowledge of its chinical pharmacology with particular attention to its respiratory effect. WENDEL, SHEMANO and ROSS said that phenazocine possessed, "besides analgesia, other activities specific for narcotics: respiratory depression, hypotension, colon spasm and constipation, excitation and mydriasis in cats, induction of tolerance, addiction liability and euphoria, and antagonism by *N*-allylnormorphine. In equivalent doses phenazocine was about half as depressant to respiration and blood pressure (anesthetized dog), two-thirds as spasmogenic on the colon (dog), and about one-third as constipating (rat). Furthermore, in a cross-over study none of 12 dogs vomited after phenazocine, while 40–75 per cent had emesis after equivalent morphine doses. The same analgesic doses of both drugs protected dogs from i.v. apomorphine- and intragastric copper sulphate-induced vomiting. In rats phenazocine caused similar but somewhat slower analgesic tolerance than morphine."

TEDESCHI, TEDESCHI and FELLOWS⁽⁵⁶⁾ compared some neuropharmacologic properties of phenazocine and morphine in mice, rats, dogs and monkeys as related to analgesia. In the rat phenazocine was approximately 25 times as potent as morphine by the tail withdrawal procedure. Orally phenazocine was only twice as potent as morphine as an analgesic. Other procedures revealed other quantitative separations in activity. Phenazocine was 12 times as potent as morphine in producing catalepsy, 10 times as potent in depressing spontaneous motor activity and 7 times as potent in blocking the conditioned escape response. Both phenazocine and morphine were effective anti-tussives in the dog and approximately equal in this respect. Nalorphine antagonized the catalepsy-producing effects of phenazocine and morphine. The overt effects produced by both drugs in the mouse, rat, rabbit and dog were quitc similar, essentially signs of central nervous system depression. In the monkey, however, morphine also depressed, but phenazocine intravenously produced no effect or signs of central nervous system stimulation.

ORAHOVATS[†] repeated much of the above pharmacological study of phenazocine with generally confirmatory results. His conclusions were as follows: Administered subcutaneously it was 8 times more potent than morphine as an analgesic in rats, 6-7 times more potent in dogs. It had poor oral activity; its ratio of subcutaneous to oral activity was about 1:20 to 1:30. The side reactions, such as general sedation and depression, hypnosis, hind-leg weakness, miosis, lowering of body temperature, were considerably milder and less frequent than those of morphine in equipotent doses. Regardless of the route of administration or the dose, phenazocine did not induce emesis or signs of nausea. The cardiovascular effects, lowering of blood pressure and slowing of the heart in dogs, were similar to those of morphine, but only very mild and transitory depression of respiration was produced (cats). Short-term chronic tests in rats indicated that tolerance to the analgesic effect developed slowly and to a mild degree. Nalorphine readily reversed both the analgesic and side-effects of phenazocine.

CARTER and DAVID⁽⁵⁷⁾ demonstrated tolerance and cross tolerance in rats of about equal degree for the analgesic effect of phenazocine, morphine and pethidine. In a later report⁽⁵⁸⁾ the same authors said that tolerance to an analgesic effect in rats developed most rapidly and to greatest degree with morphine, less with pethidine and racemoramide, and least with phenazocine. Pre-injection of phenothiazines before the analgesic drugs significantly decreased the rate of development of tolerance and hastened recovery during withdrawal. This change was least apparent with phenazocine.

Respiratory depression is an outstanding disadvantage with morphine so that its possibility becomes a major consideration with any new analgesic. Some of the experimental results indicated that relative to analgesic potency phenazocine was less likely than morphine to depress respiration and consequently a number of investigators have carried out carefully controlled and instrumental studies on this point employing in the main normal volunteers and making comparisons with morphine or pethidine.

BELLVILLE et al.⁽⁵⁹⁾ employed a modification of the re-breathing method of ECKENHOFF, HELRICH and HEGE⁽⁶⁰⁾ in nine normal subjects, obtaining the alveolar ventilation- p_{CO_2} response curve automatically. They compared 5 and 10 mg of morphine with graded doses of phenazocine, 1·5 and 3·0 mg or 1·0 and 2·0 mg or in one case 0·75 and 1·5 mg. They estimated phenazocine to be 6·4 times as potent as morphine in the production of respiratory depression. Since they had found the new drug to be three to four times as potent as morphine as an analgesic this was a result not favorable to phenazocine.

GREISHEIMER *et al.*⁽⁶¹⁾ compared phenazocine, pethidine and placebo (normal saline) in 16 normal subjects under conditions of normal and re-breathing

for effects on alveolar ventilation and carbon dioxide tension. Each subject was his own control. The doses were 2.0 mg per 70 kg weight for phenazocine and 80 mg per 70 kg for pethidine injected slowly into a continuous 5 per cent dextrose infusion. Alveolar carbon dioxide tension during normal breathing was elevated after both drugs and alveolar ventilation during rebreathing as well as during normal breathing was decreased. The percentage changes were for phenazocine and pethidine, respectively. -35.8 and -28.4 during normal breathing and -55.6 and -42.0 during rebreathing, not significantly different for the former, just significantly greater for phenazocine for the latter.

BERKOWITZ, RODMAN and CLOSE⁽⁶²⁾ also studied the respiratory effect of phenazocine employing young and elderly normals and clderly patients with cardiovascular, pulmonary or hepatic diseases. The criteria of ventilatory activity used were respiratory rate and minute volume breathing air and in response to 4 and 6 per cent CO_2 , the arterial blood p_{CO_2} , pH and oxygen saturation. In groups of five normal subjects each, a dose of 4 mg of phenazocine was compared with 15 mg of morphine and 1.5 mg of oxymorphone. There was no cross-over. The authors concluded that phenazocine depressed respiration more than either of the other narcotics. The effect of phenazocine was more marked in the clderly.

PAPADOPOULOS and KEATS⁽⁶³⁾ also compared phenazocine and morphine in the same five normal adult males, employing doses of 2.5 and 10 mg per 70 kg weight, respectively. They measured respiratory rate and minute volume, alveolar p_{CO_2} and responses to 2, 4 and 6 per cent CO₂. They constructed stimulus-response curves for both drugs at 60 and 180 min after administration. The depressant effect 1 hr after phenazocine was less than after morphine but was still present at 3 hr, whercas the effect of morphine had begun to wane. The difference at 1 hr was probably not clinically significant.

To conclude these accounts of the respiratory depressant effect of phenazocine, it may be noted that MCEWAN⁽⁶⁴⁾, using the drug for supplementation of nitrous oxide-oxygen anesthesia found it necessary to administer Levallorphan in 10 of 51 patients because of the occurrence of undue depression of respiration. In another series of 43 patients he was partially successful in avoiding respiratory depression by giving Levallorphan before the first dose of phenazocine.

After experiments on dogs in which phenazocine and pethidine produced comparable respiratory depression but the former less, indeed little, effect on the circulation, STEPHEN and MACMILLAN⁽⁶⁵⁾ gave phenazocine intravenously to 124 surgical patients, prior to induction of anesthesia, to reinforce scdation and analgesia during regional and spinal anesthesia and as an adjunct to nitrous oxide-oxygen anesthesia. Usually intermittent doses of 0.25 to 1.0 mg were given, but in 10 cases a continuous infusion of 1.0 mg per 100 ml of 5 per cent dextrose solution was used. The authors stressed that phenazocine was a potential respiratory depressant, a potentiality which was

enhanced and became of real significance when the drug was used in association with a short-acting barbiturate. STEPHEN and MACMILLAN emphasized the sparing effect of phenazocine with respect to the circulation as compared with pethidine. During their clinical use of the drug the blood pressure was remarkably stable and it was their belief that phenazocine had no depressant effect on myocardial function.

Recently CILIBERTI, SHROFF and EDDY⁽⁶⁶⁾ completed a study of phenazocine, 2 mg per 60 kg body weight, as pre-anesthetic medication in comparison with morphine, pethidine and a placebo on a double-blind basis on the surgical services of two large hospitals. There were 245–250 patients in each drug group. The resident anesthetists conducted the study and rated phenazocine nearly as effective as morphine or pethidine. It produced fewer side effects and notably no more effect on circulation than placebo, whereas there were hypotensive episodes after morphine (2) and after pethidine (7).

Two additional pieces of evidence on the clinical pharmacology of phenazocine are noteworthy and there are a number of additional reports on its clinical effectiveness. LUSTGARTEN *et al.*⁽⁶⁷⁾ tested phenazocine against morphine for anti-diuretic effect in normal individuals and in mothers with congestive heart failure. An undisturbed water or mercurial diuresis for each patient constituted the control. Morphine or phenazocine was then given on different days to these same subjects after diuresis was established. Fractional urinary volumes and electrolyte excretions were measured in each run. Both morphine and phenazocine produced an inhibition of both types of diuresis. It was postulated that phenazocine, like morphine, inhibited diuresis by increasing the output of antidiuretic hormone.

WALLENSTEIN *et al.*⁽⁶⁸⁾ reported a comparison of morphine and phenazocine with respect to subjective effects and performance in six normal subjects. The doses were 5 and 10 mg for morphine and 1 and 2 mg or 1.5 and 3 mg for phenazocine, administered intramuscularly, double blind in random order. Subjective side effects occurred much more frequently with both drugs than had been the case previously in patients with pain. Some types of performance were depressed by both drugs and phenazocine was three to seven times more potent than morphine in this depression.

In 1960 PREVOZNIK and ECKENHOFF⁽⁶⁹⁾ published a follow-up of the latter's first report, dealing with the use of phenazocine in 778 surgical patients. The drug was used for premedication in 60. The dose was 1.5 or 2.0 mg intramuscularly. Fifty-two patients appeared calm and relaxed prior to induction and nausea occurred in only 2. In 323 patients phenazocine was used as an adjunct to anesthesia in 0.5 mg doses injected intermittently into the five per cent dextrose infusion. In all but 15 patients the effect sought by the anesthetist was attained — supplementation of general anesthesia with nitrous oxide and thiopental, decrease of the thiopental requirement, or diminution of respiratory effort when controlled respiratory techniques were being employed. A fall in blood pressure occurred three times but

only from a hypertensive to the normal range. Respiratory rate slowed in eight patients but the slowing was not appreciable and respiratory assistance was not required. In the recovery room phenazocine in doses of 0.5-1.5 mg was administered 162 times for post-operative restlessness and 165 times for post-operative pain with good to complete relief in 87 per cent for the former and 80 per cent for the latter. Six patients became nauseated and six retched. For two months phenazocine was the sole narcotic used on one surgical service. Sixty-eight patients received one or more doses per day, ranging from 1.0 to 6.0 mg with good to complete relief in more than 95 per cent. Nausea or vomiting was reported for only 3 patients. The authors said in conclusion, "Evidence of circulatory and respiratory depression was observed, but the incidence of such reactions has been small. The drug was used in hypotensive states without further lowering of blood pressure." Two cases of prolonged administration were mentioned. In one 3.0 mg doses were given two or three times a day for 8 weeks with no untoward effects when the drug was abruptly withdrawn. In the other the dose was 4.0 mg two or three times daily for eight weeks without signs of dependence or tolerance.

LEAR et al.⁽⁷⁰⁾, like the preceding authors, used phenazocine for premedication, for supplementation and for immediate post-operative pain. They compared it with dextromoramide and pethidine. For premedication 102 patients received dextromoramide 1.25-5.0 mg. Phenazocine was administered to 104 patients in doses of 0.5-2.0 mg. An additional comparison was with a group of 150 patients who had received pethidine 25-100 mg. Both phenazocine and dextromoramide produced a lesser degree of adequate sedation, 55.0 and 49.5 per cent, respectively, than pethidine or morphine, 65.5 and 69.5 per cent. Neither of the new analgesics caused nausea, vomiting or disorientation; each, as well as pethidine, produced some hypotension, 8 per cent in each study group. Phenazocine and dextromoramide were employed as adjuncts to nitrous oxide anesthesia in a combined series of 380 cases. After induction the drugs were injected intravenously and repeated as necessary; detromoramide 0.5-1.0 mg, maximum 7.5 mg; phenazocine 0.2-0.4 mg, maximum 7.0 mg. Clinical management of the patients was similar so that anesthetist was unable to distinguish between the drugs when given as unknowns. In the immediate post-operative period in the recovery room 150 patients received dextromoramide intramuscularly 1.25-5.0 mg, 215 patients received phenazocine 0.5-2.0 mg and 160 patients received pethidine 25-100 mg. Phenazocine and dextromoramide were most rapid in onset of pain relief; phenazocine longest and dextromoramide shortest in duration of action. There was least evidence of hypotension and least nausea with phenazocine, most with pethidine.

SADOVE *et al.*⁽⁷¹⁾ and CORBIT and FIRST⁽⁷²⁾ have reported on the use of phenazocine in labour. The former gave the drug intravenously in doses of 1.0-4.0 mg to 202 patients. A good or excellent result was obtained in 80 pcr cent. There was delay in cry or respiration in 22-205 infants, only in

seven at all related to phenazocine. The average Apgar rating was 8.9. All depressed infants recovered uneventfully. Using a double blind technique CORBIT and FIRST compared pethidine 80 mg with phenazocine 2.0 mg administered intramuscularly. Both drugs produced adequate sage analgesia; there was no statistical difference in their efficacy. The Apgar scores for infants in the two drug groups were almost identical.

In this connection, SNYDER⁽⁷³⁾ found that phenazocine, like other narcotic analgesics given to pregnant rabbits at term, depressed fetal respiration and interfered with the labour mechanism to an extent that increased fetal mortality. Reporting on fetal mortality in at least 200 births per drug, he found the percentage results to be — non-injected controls 6, phenazocine 0.4 mg/kg 20, morphine 13.0 mg/kg 35, methadone 6.0 mg/kg 19, and pethidine 40.0 mg/kg 18. With any of these drugs the depression of fetal respiration could be removed and per cent fetal mortality decreased by the administration of nalorphine \dagger .

Young, BROWN and SMITH⁽⁷⁴⁾ undertook the trial of phenazocine as premedication for surgery in children and reported 318 cases. It was always given with scopolamine and the dose was 0.015 mg per pound weight for tonsilectomies and 0.02 mg per pound for other cases. Sedation was good but not profound, satisfactory in 80 per cent. The excellent analgesia permitted surgery in a lighter plane of anesthesia. The possibility of respiratory depression was the principal difficulty, largely avoided, however, by careful attention to the plane of anesthesia.

The Medical Division of Smith, Kline and French Laboratories \dagger reported on the oral use of phenazocine for acute and chronic pain in 980 patients. Moderate to complete relief was obtained without concomitant medication in 85·2 per cent. The dose varied from 2·0 to 10·0 mg. In more than 75 per cent relief was of 4 hr or more duration. Sedation, in addition to pain relief was noted in small numbers only 7 per cent at the 2·0 mg dose, 18 per cent at 10 mg. Side-effects, most frequently nausea and/or vomiting and dizziness, increased with increase in dose, 5 per cent at the lowest 2·0 mg, 30 per cent at the highest 10·0 mg dose.

COCHIN[†] and the authors of this report mainly through the clinical facilities of the National Institutes of Health, have assisted in the handling of many pain problems, through the use of oral phenazocine. These were cases of chronic, moderate or moderately severe pain in ambulatory or semi-ambulatory patients, getting inadequate relief on other medication or relief at the cost of excessive side effects. The dose most often employed has been $2\cdot 0$ or $2\cdot 5$ mg and most have been relieved with negligible incidence of side effects. As in the previous series higher doses have been given at the cost of more side effects. It is our conclusion that most or many ambulatory patients with acute or chronic pain can get relief of good duration with a $2\cdot 0$ or $2\cdot 5$ mg dose of phenazocine and practically no side effects. If these dose levels fail

other measures for relief should be employed and not an increase in the phenazocine dose.

In support of this conclusion DAVID and PORTER⁽⁷⁵⁾ reported the use of phenazocine orally for extended periods in doses of 2.5-10 mg. They said that the drug provided effective analgesia with a duration of effect of about 4 hr in dosages of 2.5-5.0 mg three or four times a day. The incidence of side effects was very low. On the other hand, LASAGNA and DEKORNFELD[†] gave phenazocine orally to post-partum patients with very poor results. The dose was 5 mg in 30 patients and 10 mg in 28 patients. There was no difference in the relief afforded by these two doses and this was only a little better than was seen with a placebo. However, side effects were more frequent with the larger dose; one vomited, two complained of dizziness and eleven of sleepiness. This discordant result may very probably be related to the type of pain for which relief was sought.

One additional note about the clinical use of phenazocine has come to our attention. KURLAND and GRUENWALD⁽⁷⁶⁾ administered the drug orally or subcutaneously for periods of 2-100 days to 14 female patients with depression as part of their symptomatology, residing on the chronic wards of a psychiatric hospital. No significant improvement could be found in any patient even with the maximum dosage utilized, 20-30 mg/day. The greater the degree of depressive effect in the patient, the worse they seemed to become on this medication. In a few patients there appeared to be a transient diminution of their tension. Nausea and vomiting were seen in six patients and a rash in one.

The crucial question in the clinical use of phenazocine is its likelihood to produce tolerance and physical dependence. Mention has been made of the work in monkeys which indicated a separation of analgesic and physical dependence properties; and some evidence of a slower development of tolerance with phenazocine has been alluded to. Using their established techniques of single dose administration for morphine-like effects in post-addicts, 24-hr substitution in stabilized morphine addicts and direct addiction experiments, FRASER and ISBELL⁽⁷⁷⁾ studied extensively in their post-addict population the addiction and abuse liability of phenazocine. They found that in single doses subcutaneously or intravenously it produced pupillary constriction and other morphine-like effects; 40 mg subcutaneously was approximately equivalent to 13.0 mg of morphine in the production of subjective effects. Phenazocine was completely adequate as a substitute for morphine in stabilized morphine addicts and was more potent, 1 mg being equivalent to 8.15 mg of morphine. Phenazocine produced physical dependence resembling that caused by morphine in direct addiction experiments but this appeared to be milder and to develop more slowly. Notably in these direct addiction attempts the dose of phenazocine could not be increased as rapidly nor proportionately to the same extent as could be done with morphine.

Other benzomorphans which have been tested for analgesic effectiveness in man are (-)-2'-hydroxy-2,5,9-trimethyl-6,7-benzomorphan (59), (\pm) -5,9-diethyl-2'-hydroxy-2-methyl-6,7-benzomorphan (34.2), (\pm) -2'-methoxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan (54.2) and some of the specific antagonists (see the section on antagonists for the latter). The first of these (59) had an ED₅₀ for analgesic effect in mice of 1.7 mg/kg subcutaneously, in the morphine range, probably slightly more potent. In the monkey physical dependence capacity was very low up to 50 mg/kg subcutaneously and the compound produced no significant toxic effects on chronic administration to rats (BYWATER †).

LASAGNA[†] administered this compound subcutaneously to patients with post-operative pain in doses of 3–15 mg and compared the results with those of 10 mg of morphine on the basis of the effect of first doses per individual and of total effect. He concluded that a dose of 15 mg was as good as or perhaps somewhat better than 10 mg of morphine in pain relieving power. No untoward effects of any consequence were seen.

FRASER and his associates⁽⁷⁸⁾ studied the addictiveness in man of (-)-2'hydroxy-2,5,9-trimethyl-6,7-benzomorphan (59), concluding that it was somewhat less than that of morphine. An unusual variation in the effects of this drug was noted. On one cross-over double blind experiment single doses of 20 mg of (59) were compared with 20 mg of morphine sulphate in drugfree postaddicts. A typical and very similar morphine-like pattern of effects was demonstrated in this test for both drugs. This was confirmed in a second experiment in which 12 and 24 mg of (59) were compared with 15 and 30 mg of morphine. All of these doses were given subcutaneously and indicated that, in single doses to post-addicts, (59) was at least as potent as morphine. In the next experiment, however, its potency was much less. It was substituted for morphine for 24 hr in subjects stabilized on morphine, 240 mg per day. The doses of (59) were 110 mg (2 subjects), 160 mg (3 subjects) and 360 mg (5 subjects) in place of the usual 180 mg of morphine for the same period. As a substitute (59) was not much better than a placebo. FRASER et al. estimated its potency in this respect as only one-eighth that of morphine. This low potency as a substitute in contrast to approximate equivalence to morphine as an analgesic in animals and man and in the production of morphinelike subjective effects suggested a partial dissociation of morphine-like analgesic and physical dependence properties, so that a direct experimental addiction experiment was undertaken. This was a cross-over experiment with five subjects. In one part the subjects received morphine sulphate in increasing dosage, easily reaching 240 mg per day in 18 days and being maintained at that level through the 25th day. In the other part the same subjects received the benzomorphan (59) but it was possible to increase the dose only to 180 mg per day in 18 days (toxic effects occurred with higher doses) which was maintained through the 25th day. During the experimental addiction

all subjects consistently identified both drugs as "dope" and potency ratings were similar. Positive responses to the question, "Would you like to take this drug every day?" were the same, 32 per cent for both drugs, but negative responses were only 14 per cent for morphine and 55 per cent for the experimental drug. Also only 1 per cent of the time was morphine said to make the subject feel bad while the response on this point was 26 per cent feel bad with the benzomorphan. When the drugs were abruptly withdrawn the intensity of abstinence signs was less in peak on the second day and in total with (59) than with morphine. Relatively peak scores were 23.5 and 34.8 and total scores 147.9 and 209.1.

FRASER et al. point out that heretofore single dose substitution and direct addiction procedures have shown reasonably good agreement as tests to determine the degree of addiction liability. However, in the present case, although (59) was as potent as or slightly more potent than morphine in single doses in post-addicts, it was only about one-eighth as potent as morphine in suppressing signs of abstinence in patients dependent on morphine. Nevertheless the degree of abstinence observed following abrupt withdrawal of (59) in a direct addiction attempt was greater than would be predicted from the substitution test. These results suggest the advisability of experimental direct addiction evaluation when the previous results with a compound are not consistent. The results with (59) also confirm what was shown with phenazocine that the tests with benzomorphans in monkeys cannot serve to predict addiction liability in man, except that within the group itself relative potency of members of the group in the monkey parallel generally relative potency of those members for analgesia in animals and for effects in man.

LASAGNA and DEKORNFELD[†] have tested (34.2) as well as (59) for analgesic effectiveness against post-operative pain in man and (54.2) administered orally against post-partum pain. The former was only half as effective as morphine as an analgesic by the hot-plate method in mice and had no physical dependence capacity (abstinence suppressant potency) in monkeys up to 60 mg/kg subcutaneously. Administered daily to monkeys in doses increasing from 5 to 30 mg per kg subcutaneously in 31 days its physical dependence properties were very low. According to LASAGNA and DEKORNFELD (34.2) at a dose of 10 mg alternating with 10 mg of morphine has a similar onset and duration of action, but an inferior peak analgesic effect. At a 20 mg dose alternating with 10 mg of morphine subcutaneously in 20 post-operative patients (34.2) was definitely superior in peak analgesic effect through 4 hr of observation. The morphine equivalent analgesic dose would, therefore, lie between 10 and 20 mg, a good carryover from the laboratory observation. The only untoward reaction was a vomiting episode in one patient receiving the 20 mg dose, but such an episode occurred also in one patient who received 10 mg of morphine.

In post-partum patients 20 mg of (54.2) was administered orally and compared with 600 mg of aspirin and a placebo. Both (54.2) and aspirin were superior to the placebo and the former was better than aspirin in bringing about pain relief especially at 3 and 4 hr after administration. Unfortunately, the incidence of side effects with (54.2) was high. Of 34 patients who received this compound 14 complained of one or more side effects (dizziness, nausea, vomiting, anorexia, pruritus, sleepiness, lightheadedness and hypotension), whereas aspirin and the palcebo were virtually free of side effects. These patients were ambulatory or semiambulatory which may have increased the incidence of untoward reactions. The solubility of (54.2) was too low to permit its trial other than orally. Its ED_{50} for analgesic effect in mice was 10 mg per kg subcutaneously and it had no physical dependence capacity in monkeys up to 60 mg/kg.

CHAPTER V

Opiate Antagonists in the Benzomorphan Series

THE structural relationship of benzomorphans to morphine and morphinan derivatives led naturally to N-allyl and related substitutions in various benzomorphan structures. GORDON et al.⁽⁷⁹⁾ described the synthesis of 2-allyl-2'hydroxy-5,9-dimethyl-6,7-benzomorphan (SKF 10, 047, nalorphine analog) and of 2-allyl-2'-methoxy-5,9-dimethyl-6,7-benzomorphan. ARCHER and his associates⁽⁴²⁾ prepared and studied some 25 compounds of this sort, a series in which the substituent at 2 of benzomorphan was modified in a manner more or less comparable to previous work on morphine and morphinans. A few of these compounds were examined in our laboratory. The pharmacology of some of them was described by ARCHER et al.⁽⁴²⁾ and by HARRIS and PIERSON⁽⁸⁰⁾. The Sterling-Winthrop Laboratories have kindly supplied us with data[†] on the whole series. (See Tables XXXIV and XXXV). Some of these compounds too have been tested in monkeys for antagonistic (Nalorphine-like) action and/or physical dependence capacity and some arc under investigation in man for analgesic effect, side action liability and morphinelike properties in post-addicts.

This group of "antagonists" had little demonstrable analgesic action in animals, but they did have the property of antagonizing, reducing or abolishing the analgesic effect of other powerful analgesics. All have been tested on this point against one or all of the trio; pethidine, morphine and phenazocine. In Tables XXXIV and XXXV, the compounds have been arranged in the order of their chemical relationships and their antagonistic potency varies widely, from materially less to several times greater than that of nalorphine. The rank order (figures in parentheses, Table XXXV) of their antagonistic action, however, against the analgesic effect of pethidine, morphine or phenazocine is much the same, suggesting a common mechanism of action. So far as they have been tested the secompounds, like Nalorphine or Levallorphan, have the ability to reverse in similar degree the respiratory and behavioral effects of the morphine-like analgesics.

In the section on the chemistry of the benzomorphans, it was pointed out that the 5,9-disubstituted derivatives could exist in *trans*-(α -) or *cis*-(β -) form. Generally a marked difference in the analgesic activity in animals of the two forms was demonstrated. Win 20,228 and Win 20,740 as shown in the tables have the α -configuration. ArcHFR and his associates prepared the corres-

+ Including some unpublished.

ponding β -compounds. Win 20,228 and Win 20,740 differed widely in antagonistic potency, their β -isomers did also. However, the difference between the α - and β -forms of the two compounds, respectively, was small and probably hardly significant. The AD₅₀ against the analgesic effect of pethidine was 3.9 for α -Win 20,228 and 3.3 mg/kg for β -Win 20,228. Similarly, the AD₅₀ was 0.019 for α -Win 20,740 and 0.011 mg/kg for β -Win 20,740. This is a most interesting variation in structure action relationships.

LASAGNA and BEECHER⁽⁸⁴⁾ in 1954 and KEATS and TELFORD⁽⁸⁵⁾ in 1956 showed that Nalorphine, in spite of its specific opiate antagonistic action, could effect relief of post-operative pain was well as morphine on a mg for mg basis. Unfortunately the relief was accompanied by bizarrc subjective reactions, very disturbing to the patient. However, the wide range of antagonistic potency, seen first with morphine and morphinan derivatives and now also in the benzomorphan series, suggested that among the antagonists there might be an effective analgesic which produced little or none of the disturbing Nalorphine-like side effects. To this end a number of the benzomorphans with specific antagonistic properties are under clinical investigation: 2-allyl-2'-hydroxy-5,9-dimethyl-6,7-benzomorphan (SKF 10,047); 2-allyl-5ethyl-2'-hydroxy-9-mcthyl-6,7-benzomorphan (Win 19,362); 2'-hydroxy-5,9dimethyl-2-(3,3-dimethylallyl)-6,7-benzomorphan (Win 20,228); 5-ethyl-2'hydroxy-9-methyl-2-(3,3-dimethylalhyl)-6,7 benzomorphan (Win 20,264); and 2-cyclopropylmethyl-2'-hydroxy-5,9-dimethyl-6,7-benzomorphan (Win 20,740).

SKF 10,047 could be used clinically as an opiate antagonist, having a potency equal to⁽⁷⁹⁾ or greater than⁽⁴²⁾ that of nalorphine. Mixtures of it with phenazocine in various ratios have been studied for analgesic activity and physical dependence capacity⁽⁷⁹⁾. A 1:1 mixture produced no analgesia in animals and precipitated abstinence phenomena in morphine-dependent monkeys. With a ratio of nine parts of phenazocinc to one of the antagonist, the analgesic effect in animals was as good as with phenazocine alone but there was again precipitation of abstinence signs in addicted monkeys, as seen with nalorphine, instead of suppression. Mixtures of 25:1 and 50:1 acted similarly; with a 100:1 mixture there was neither precipitation nor suppression of abstinence signs up to 16 mg/kg. SNYDER † has reported to us that, whereas phenazocine alone has a morphine-like effect on the labor mechanism in pregnant rabbits at term and increases fetal mortality to about 20 per cent, phenazocine plus SKF 10,047 in a 50:1 ratio appeared to have no effect on the labor mechanism and fetal mortality was in the normal range, about five per cent.

The retention of analgesic effectiveness in man comparable to that of phenazocine alone was demonstrated by KEATS[†] in post-operative patients for the 9:1 mixture but the same mixture did not abate the development of physical dependence in man (FRASER[†]).

SKF 10,047 alone had an analgesic effect against post-operative pain in man somewhat less than that of morphine or Nalorphine. Fifteen milligrams of it was not as effective as 10 mg of morphine. Higher doses were not tried because Nalorphine-like disturbing subjective effects were seen in some patients (KEATS⁺).

Win 19,362 was about three times as potent as Nalorphine as an antagonist and about twice as potent as morphine as an analgesic in post-operative pain. However, this compound, in doses of 5 and 10 mg, produced severe side effects, including psychic reactions such as had been seen with nalorphine, precluding its further clinical trial⁽⁴²⁾.

Win 20,228 and Win 20,264 differ from each other only in the substituent at position 5, methyl in the former, ethyl in the latter. Both are weak opiate antagonists and both are analgesics in post-operative pain in man, in the dosage range of 20–40 mg. Potency estimates by different observers are fairly consistent; equivalence to 10 mg of morphine is not less than 20 mg, probably more nearly 30 mg per 70 kg body weight. Nalorphine-line subjective effects have not been seen with Win 20,228; such side-effects as were seen were like those occurring commonly with morphine and were not more severe than with morphine (42.86).

Win 20,228 at a dose of 20 mg produced some respiratory depression which was comparable in degree to that of 10 mg of morphine and which was not antagonized by nalorphine. Increasing the dose did not result in apnoea (KEATS †). In contrast to morphine Win 20,228 in doses greater than 2 mg/kg intravenously produced tachycardia and hypertension.

Because of its analgesic effectiveness and the absence of nalorphine-like subjective effects Win 20,228 was tested at the Addiction Research Center, Lexington, Ky. (FRASER and ROSENBERG⁽⁸⁷⁾). The subjective effects following single doses up to 50 mg in post-addicts differed qualitatively from those of morphine. Also in 24-hr substitution for morphine in individuals stabilized on 240 mg of the latter per day, Win 20,228 even in larger doses (360 mg per day) was disliked by the subjects and had little effect on the morphine abstinence syndrome. In an attempt at direct addiction, only one of three subjects would continue the administration of Win 20,228 for the planned 25 days, attaining a dose of 385 mg per day. There was marked irritation at the site of injection. Abrupt withdrawal of the drug resulted in mild abstinence signs, in marked contrast to the result of a similar schedule of morphine administration in the same individual. FRASER and ROSENBERG concluded that Win 20,228 had no significant degree of morphine-like addictiveness.

Win 20,740 is a most interesting compound. It was the most potent antagonist tried in the benzomorphan series, showed some analgesic effect in animals and was a very potent analgesic in man at doses which produced no Nalorphine-like subjective effects. The latter have occurred occasionally when the dose was increased several-fold.

LASAGNA, DEKORNFELD and PEARSON[†] estimated the dose of Win 20,740 equivalent to 10 mg of morphine against postoperative pain as close to 0.25 mg. They said it was also effective by mouth; 0.25 mg was equivalent to the usual dose of Darvon compound (dextropropoxyphene 65 mg plus an APC mixture) against post-partum pain. Win 20,740 has produced symptoms of drunkenness, confusion and unpleasant subjective effects, but in only one person who received a dose of less than 1.0 mg parenterally or by mouth.

Preliminary results at the Addiction Research Center with Win 20,740 (FRASER and ROSENBERG[†]) showed that single doses, orally, subcutaneously or intravenously produced occasionally effects identified as opiate-like. The doses used were 1.0 mg orally, 0.4 and 0.8 mg subcutaneously and 0.1 to 0.6 mg intravenously. Comparison was with 10 and 20 mg of morphine subcutaneously. Substituted for morphine in individuals stabilized on 240 mg of morphine per day, Win 20,240, like Nalorphine or Levallorphan and comparable to them in potency, precipitated rather than suppressed abstinence phenomena. Administered chronically for 25 days Win 20,740 induced initially some dysphoria to which tolerance developed and was seldom identified as an opiate. When the drug was abruptly withdrawn a very mild atypical abstinence syndrome developed, whereas the same patients showed moderate to severe abstinence phenomena after a comparable direct addiction to morphine.

CHAPTER VI

Summary

LAEVO-3-hydroxy-*N*-methyl-morphinan, a structure lacking the characteristic oxygen bridge and 6-carbon substituent of the morphine molecule, proved to be a more effective analgesic than morphine, but not qualitatively or essentially different. Obviously the complete morphine structure was not obligatory for a high degree of activity and investigation of further simplification was in order. The benzomorphans resulted, a step further from morphine in their structure through scission of ring C and retention of only an alkyl residue to preserve the quaternary carbon in the same relation to nitrogen as in morphine or morphinan.

The series of benzomorphans has been extended to well over 100 with particular attention to the substituent at 2',2,5 or 9. Where the chemical changes parallel those previously described in the morphine and/or morphinan series, relationships have been discussed. The following generalizations are believed to be justified:

1. The structure-activity relationships for changes at 2' or 2 for the most part run parallel in the morphine, morphinan and benzomorphan series.

2. Introduction of an hydroxyl at position 9 (corresponding to carbon-14 of morphine or morphinan) decreases generally analgesic action, whereas similar substitution in morphine or morphinan increased it notably.

3. In all three series analgesic properties are exhibited predominantly by the *laevo*-isomer. In the stereoisomeric pairs of benzomorphans with respect to the substituent at 9, significantly greater activity and a better toxicity-analgesic action ratio are seen generally with the β -(cis-) form.

4. Physical dependence capacity of benzomorphans in the monkey is generally low, especially relative to analgesic potency, but this characteristic has not carried over well to man. In one instance, however, a benzomorphan [(-)-2'-hydroxy-2,5,9-trimethyl-6,7-benzomorphan] has been in man as effective as morphine in the production of morphine-like subjective reactions but has been only one-eighth as effective in suppression of morphine abstinence phenomena (substitution in morphine-dependent individuals) and has apparently produced less physical dependence during chronic administration.

5. Suitable substitution on nitrogen of benzomorphan, as in the morphine or morphinan series, can enhance analgesic effectiveness or result in the appearance of antagonistic properties. Some at least of the antagonists in the benzomorphan series are analgesics in man against various types of pain and may exhibit such favorable action without marked respiratory depression or bizarre, disturbing side effects.

6. The benzomorphans as a class are morphine-like but there are quantitative differences which suggest that some dissociation between useful and undesirable properties is being attained.

						Observations on monkeys		monkeys
No.	See Table	Substituent at 2'	Other substituents	ED₅0†	LD ₅₀ †	Morphine		ne
				_		PDC	Equiv.	Dose range
9	XIX	Н	2,5-Dimethyl-	22.1	148			
10	XIX	OH	2,5-Dimethyl-	10.4	175	none		2-60 (1)
29.1	XX.	H	α-2,5,9-Trimethyl	27.3	155			
29.3	XX	OH	α-2,5,9-Trimethyl	3.0	175	low	24.0	3-24 (2)
29.2	XX	OCH ₃	α-2,5,9-Trimethyl	9.8		low	none	2.5-10 (3)
50.1	XX	OCOCH ₃	a-2,5,9-Trimethyl	1.17	ca. 200	intermed.	>12.0	1-12 (4)
35.6		Н	β -2,5,9-Trimethyl	8.9	178			
35.1	XXI	OH	β -2,5,9-Trimethyl	0.44	67	low	>18.0	0.5-18 (5)
29.4		Н	α-5,9-Diethyl-2-methyl	5-0	83	none		1-16 (6)
34.2		OH	α-5,9-Diethyl-2-methyl	4.2	423	none		2-60 (7)
34.7	XX	OCOCH ₃	α-5,9-Diethyl-2-methyl	3.0	252	none		2-32 (8)
35.7	XXI	H	β -5,9-Diethyl-2-methyl	4.2	ca. 80			
35.2	XXI	OH	β -5,9-Diethyl-2-methyl	0.28	ca. 110	none		0.5-12 (9)
42.4	XXII	H	α-9-Hydroxy-2,5-dimethyl	63.8	>400			
42.8	XXII	OH	α-9-Hydroxy-2,5-dimethyl	79.9		1		
42.6	XXII	OCH ₃	α-9-Hydroxy-2,5-dimethyl	>100.0	>200	1.		
45.5		H	β -9-Hydroxy-2,5,9-trimethyl	112.1				
45.9	XXIII	OH	β -9-Hydroxy-2,5,9-trimethyl	6.0	55			
45.7	XXIII	OCH ₃	β -9-Hydroxy-2,5,9-trimethyl	I	63			
42.14	XXIV	Н	α -9-Acetoxy-2,5-dimethyl	29.0	367			
42.15	XXIV	OCOCH ₃	α-9-Acetoxy-2,5-dimethyl	0.51	>200	high	48 ∙0	0.5-72 (10)
54.6	XXV	н	5-Methyl-2-phenethyl	35.9	>400	-		
54.7	XXV	OH	5-Methyl-2-phenethyl	0.48	55	none		1-16 (6)
52.4	XXV	н	5,9-Dimethyl-2-(3-oxo-3-phenylpropyl)	8.7	>400			
		1		1	l	l		1

TABLE XXX. The effect of the substituent at position 2' of 6,7-benzomorphans

TABLE XXX— continued

					1	Observations on monkeys		monkeys
No.	See Table	Substituent at 2'	Other substituents	ED50†	LD50 [†]		e	
					l I	PDC	Equiv.	Dose range
52.3	XXV	ОН	5,9-Dimethyl-2-(3-oxo-3-phenylpropyl)	2.3	83	none		1-2 (11)
42.9	XXII	OH	α-9-Hydroxy-2,5,9-trimethyl	6.9				
42.7	XXII	OCH ₃	a-9-Hydroxy-2,5,9-trimethyl	19.7	373	very low	none	2.5-25 (12)
42.12	XXII	OH	α -5-Ethyl-9-hydroxy-2-methyl	l	>400			
42.10	XXII	OCH ₃	α-5-Ethyl-9-hydroxy-2-methyl	67.4	<i>ca</i> . 400			
42.13	XXII	OH	α-5-Ethyl-9-hydroxy-2,9-dimethyl	6.7	>300			
42.11	XXII	OCH ₃	α -5-Ethyl-9-hydroxy-2,9-dimethyl	13.8	> 200			
45.8	XXIII	OH	β-9-Hydroxy-2,5-dimethyl		>200			
45.6		OCH ₃	β-9-Hydroxy-2,3-dimethyl	4/.3	<i>ca.</i> 100			
42.19	XXIV	OH	a-9-Acetoxy-5-ethyl-2,9-dimethyl	1.13	<i>ca</i> . 400			
42.18	XXIV	OCH ₃	α -9-Acetoxy-5-ethyl-2,9-dimethyl	14.8	>400			
42.20	XXIV	OCOCH ₃	α-9-Acetoxy-5-ethyl-2,9-dimethyl	1.15	>400			
42.17	XXIV	OCH ₃	α -9-Acetoxy-5-ethyl-2-methyl	22.6	197]
42.21	XXIV	OCOCH ₃	α -2,9-Diacetoxy-5-ethyl-2-methyl	2.2	262	hish	17.0	1 10 (12)
54.3	XXV	OH	5.9-Dimethyl-2-phenethyl	0.25	332	nign	17.0	1 - 18 (13)
54.2	XXV	OCH ₃	5.0 Dimethyl 2 nh an athal	0.2		very low	none	3-60 (13)
52.22	1000	OCH2OCH3	5.0 Dimensional 2 mb en ethyl	3.3	100	low		0.5 22 (14)
54.1		OCOCH3	5,9-Dimethyl-2-phenethyl	0.19	109	IOW	none	0.3-32 (14)
52.16	xxv	OCO	5.9-Dimethyl-2-phenethyl	0.41		low	none	0.5-32 (13)
54.9	XXVI	OH (E)	α-9-Hydroxy-5-methyl-2-phenethyl	0.62	ca. 100			
54.10	XXVI	OCH ₃	α -9-Hydroxy-5-methyl-2-phenethyl	22.2	>400			
59	XXVII	OH	(-)-2,5,9-Trimethyl	1.69	>400	very low	none	1-50 (15)
59.1	XXVII	OCH ₃	(-)-2,5,9-Trimethyl	8.7	175			
54.12	XXVII	ОН	()-5,9-Dimethyl-2-phenethyl	0.11	147	high	9.0	2-8 (13)

SUMMARY

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						Obs	ervations or	n monkeys
No.	See Table	Substituent at 2'	Other substituents	ED ₅₀ †	LD50†		Morphir	ne
						PDC	Equiv.	Dose range
54.14	XXVII	OCH3	()-5,9-Dimethyl-2-phenethyl	1.83	>500	none		2-60 (13)
52.17	xxv	oco∕_N∕	()-5,9-Dimethyl-2-phenethyl	0.17		low		2-100
75.2	XXIX	н	1,2-Dimethyl-1-(2-dimethylaminoethyl)- 1,2,3,4-tetrahydronaphthalene	41.1	411			
75.6	XXIX	ОН	1,2-Dimethyl-1-(2-dimethylaminoethyl)-	I	>600			
75.5	XXIX	OCH3	1,2-Dimethyl-1-(2-dimethylaminoethyl)- 1,2,3,4-tetrahydronaphthalene	27.1	649	low	>100.0	>100.0

† See Table XIX.

PDC = Physical dependence capacity. See text for interpretation of grades.

Morphine equiv. = Dose which equals 3 mg/kg of morphine sulfate in ability to suppress morphine abstinence syndrome. See text for calculation.

- I = Inactive; no analgesic effect seen with doses used, usually up to 100 mg/kg.
- (1) 60 mg/kg-Exacerbation of abstinence signs; no suppression at lower doses.
- (2) 6 mg/kg-Ataxia, increasing in severity with higher doses; 24 mg/kg-Disorientation and hallucinations.
- (3) 10 mg/kg-Tremor, muscular rigidity and ataxia.
- (4) 4 mg/kg-Ataxia, increasing in severity with higher doses.
- (5) 12 mg/kg-Tremor and ataxia.
- (6) 16 mg/kg-Convulsion.
- (7) 60 mg/kg-- Convulsion; some sedation but no suppression with lower doses.
- (8) 32 mg/kg-Severe dyspnoea.

- (9) 4 mg/kg--Mydriasis, widened palpebial fissures, severe intention tremor and ataxia; some decreased apprehension but no suppression of other signs.
 - 8 mg/kg-Similar symptoms in non-addicted monkeys, not antagonized by nalorphine.
- (10) 72 mg/kg-Some sedation, convulsion.
- (11) 2 mg/kg-Disoriented, unable to move limbs.
 - 1 mg/kg—Ptosis, relaxation of facial muscles, fixed staring pose, ataxia, excitability in non-addicted monkeys, not antagonized by nalorphine.
- (12) 15 mg/kg-Exacerbation of abstinence signs.
 - 25 mg/kg-Severe muscular twitching.
- (13) —No signs of toxicity reported.
- (14) 16 mg/kg-Tremor, plus disorientation at 32 mg/kg.
- (15) 30 mg/kg-Ataxia, increasing in severity with higher doses.

						Observations on monke		monkeys
No.	See Table	Substituent at 9	Other substituents	ED50†	LD50†		Morphir	ne
						PDC	equiv.	Dose range
9 29.1 35.6 42.4 42.14 42.5 45.5 10 29.3 35.1 34.4 35.4 42.8 45.8 42.9 45.9 19.8	XIX XX XXI XXII XXII XXII XXII XXII XX	H; H H; α-CH ₃ H; β-CH ₃ H; α-OH H; α-OCOCH ₃ α-CH ₃ ; OH β-CH ₃ ; OH H; H H; α-CH ₃ H; β-CH ₃ H; β-CH ₃ H; β-CH ₃ H; β-C ₂ H ₅ H; α-OH H; β-OH α-CH ₃ ; OH β-CH ₃ ; OH H; H	2,5-Dimethyl 2,5-Dimethyl 2,5-Dimethyl 2,5-Dimethyl 2,5-Dimethyl 2,5-Dimethyl 2,5-Dimethyl 2,5-Dimethyl 2'-Hydroxy-2,5-dimethyl 2'-Hydroxy-2,5-dimethyl 2'-Hydroxy-2,5-dimethyl 2'-Hydroxy-2,5-dimethyl 2'-Hydroxy-2,5-dimethyl 2'-Hydroxy-2,5-dimethyl 2'-Hydroxy-2,5-dimethyl 2'-Hydroxy-2,5-dimethyl 2'-Hydroxy-2,5-dimethyl 2'-Hydroxy-2,5-dimethyl 2'-Hydroxy-2,5-dimethyl 2'-Hydroxy-2,5-dimethyl 2'-Hydroxy-2,5-dimethyl 2'-Hydroxy-2,5-dimethyl	22.1 27.3 8.9 63.8 29.0 43.7 112.1 10.4 3.0 0.44 1.50 0.447 79.9 I 6.9 6.0 2.3	$ \begin{array}{r} 148 \\ 155 \\ 178 \\ >400 \\ 367 \\ >400 \\ - \\ 175 \\ 175 \\ 67 \\ 134 \\ 85 \\ - \\ >200 \\ - \\ 55 \\ 171 \\ 202 \end{array} $	none low low none	24.0 >18.0 none	2-60 (1) 3-24 (2) 0·5-18 (3) 1-12 (4) 2-32 (5) 2-40 (2)
34.5 35.5		H; α -CH ₃ H: β -CH ₂	5-Ethyl-2'-hydroxy-2-methyl 5-Ethyl-2'-hydroxy-2-methyl	4·9 0·07	309 60	inter-	none 60	2-40(6) 0.5-12(7)
34.2 35.2 42.12 45.12	XX XXI XXII XXIII	H; α-C ₂ H ₅ H; β-C ₂ H ₅ H; α-OH H; β-OH	5-Ethyl-2'-hydroxy-2-methyl 5-Ethyl-2'-hydroxy-2-methyl 5-Ethyl-2'-hydroxy-2-methyl 5-Ethyl-2'-hydroxy-2-methyl	4·2 0·28 I 12·2	423 ca. 110 >400 >400	mediate none none		2-60(8) 0·5-12 (9)

TABLE XXXI. THE EFFECT OF THE SUBSTITUENT AT POSITION 9 OF 6,7-BENZOMORPHANS

						Obser	rvations on	monkeys
No.	See Table	Substituent at 9	Other substituents	ED50†	LD50 [†]		Morphir	ie
						PDC	equiv.	Dose range
42.19 19.10 34.3 35.3	XXIV XIX XX XX XXI	α-CH ₃ ; OCOCH ₃ H; H H; α-C ₃ H ₇ H; β-C ₃ H ₇	5-Ethyl-2'-hydroxy-2-methyl 2'-Hydroxy-2-methyl-5-propyl 2'-Hydroxy-2-methyl-5-propyl 2'-Hydroxy-2-methyl-5-propyl	1.13 2.1 71.2 0.87	$ \begin{array}{c} ca. 400 \\ 130 \\ > 400 \\ 62 \end{array} $	low none	none	2-64 (10) 3-48 (11)

[†] For explanation of these and other data see Tables XIX and XX.

- (1) 60 mg/kg-Exacerbation of abstinence signs, no suppression at lower doses.
- (2) 6 mg/kg-Ataxia; 24 mg/kg ataxia, disorientation, hallucinations.
- (3) 12 mg/kg-Tremor and ataxia.
- (4) 4 mg/kg-Ataxia, barbiturare-like sedation.
- (5) -No signs of toxicity reported.
- (6) 40 mg/kg-Muscular weakness, salivation, dyspnoea.
- (7) 8 mg/kg—Ataxia, tremor.
 - 12 mg/kg-Coma, respiratory arrest.
- (8) 60 mg/kg-Convulsion; some sedation but no suppression at lower doses.
- (9) 4 mg/kg-Mydriasis, widened palpebial fissures, severe intention tremor and ataxia; apprehension decreased but no suppression of other signs.
- (10) 64 mg/kg-Convulsion.
- (11) 12 mg/kg-Exacerbation of abstinence signs;
 48 mg/kg-Ataxia, tremor, disorientation.

						Obser	Morphine equiv. Dose range 6-60 (1) 1-16 (2) none 2-32 (3) 16·0 0·5-16 (4) 24·0 3-24 (5)	
No.	See Table	Substituent at 2	Other substituents ⁺	ED₅o†	LD50†		Morphin	e
						PDC	equiv.	Dose range
9	XIX	CH₃	5-Methyl	22·1	148			
54.6	xxv	CH ₂ CH ₂	5-Methyl	35.9	>400			
29.1	xx	CH ₃	5,9-Dimethyl	27.3	155			
52.4	xxv	CH ₂ CH ₂ CO	5,9-Dimethyl	8.7	>400			
10	XIX	CH ₃	2'-Hydroxy-5-methyl	10.4	175	none		6–60 (1)
54.7	xxv	CH ₂ CH ₂	2'-Hydroxy-5-methyl	0.48	55	none		1-16 (2)
19.8	XXIX	CH ₃	5-Ethyl-2'-hydroxy	2.3	171	low	none	2–32 (3)
54.8	xxv	CH ₂ CH ₂	5-Ethyl-2'-hydroxy	0.16	88	inter- mediate	16.0	0·5–16 (4)
52.11 29.3 52.12 52.13 52.14 52.15 52.18	XXV XXV XXV XXV XXV XXV XXV XXV	H CH ₃ C ₂ H ₅ C ₃ H ₇ C ₄ H ₉ C ₅ H ₁₁ CH ₂ CH=CH ₂ (CH ₂ CH=CH ₂) ₂ Br $^{\ominus}$	2'-Hydroxy-5,9-dimethyl 2'-Hydroxy-5,9-dimethyl 2'-Hydroxy-5,9-dimethyl 2'-Hydroxy-5,9-dimethyl 2'-Hydroxy-5,9-dimethyl 2'-Hydroxy-5,9-dimethyl 2'-Hydroxy-5,9-dimethyl 2'-Hydroxy-5,9-dimethyl	I 3·0 I I I 2·2 I I I	$ \begin{array}{r} $	low low none	24.0	3-24 (5) 0·5-16 (2)

TABLE XXXII. THE EFFECT OF MODIFYING THE SUBSTITUENT AT 2; N-ALKYL OR ARALKYL 6,7-BENZOMORPHANS

TABLE XXXII— continued

						Obsei	Observations on monk		
No.	See Table	Substituent at 2	Other substituents +	ED50†	LD50†		Morphi	ne	
						PDC	equiv.	Dose range	
52. 2 0	xxv	CH ₂ CH==C(CH ₃) ₂	2'-Hydroxy-5,9-dimethyl	I	ca. 400	none		2-30 (6)	
5 2. 19	XXV	CH ₂ CH CH ₂ CH	2'-Hydroxy-5,9-dimethyl	23.1	>300	none		0.01-0.1 (7)	
54. 3	xxv	CH ₂ CH ₂	2'-Hydroxy-5,9-dimethyl	0.25	332	high	17.0	1–18 (8)	SUMN
5 2 .3	xxv	CH ₂ CH ₂ CO	2'-Hydroxy-5,9-dimethyl	2.3	83	none		1-2 (9)	IARY
52.6	xxv	CH ₂ CH ₂ CH ₂	2'-Hydroxy-5,9-dimethyl	13.6	-	none		2-30 (10)	
52.7	xxv	CH ₂ CH ₂ NH ₂	2'-Hydroxy-5,9-dimethyl	0.11	125	inter- mediate	0.2	0.5-3.0 (8)	
52.9	xxv	CH ₂ CH ₂ OH	2'-Hydroxy-5,9-dimethyl	(13)	-				
52.8	xxv	CH ₂ CH ₂ OCH ₃	2'-Hydroxy-5,9-dimethyl	0.32	>450	low		0·1–24 (11)	
52.10	xxv	CH ₂ CH ₂	2'-Hydroxy-5,9-dimethyl	0.055	88	low		0.25–2 (12)	
		`S /	· · · · · · · · · · · · · · · · · · ·						169

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						Observations on monkeys			
No.	See Table	Substituent at 2	Other substituents ⁺	ED50†	LD50 [†]	Morphine			
						PDC	equiv.	Dose range	
29.2	xx	CH₃	2'-Methoxy-5,9-dimethyl	9•8	-	low		2.5-10(13)	
54.2	xxv	CH ₂ CH ₂	2'-Methoxy-5,9-dimethyl	6.5	_	very low		3-60 (8)	
50.1	xx	CH ₃	2'-Acetoxy-5,9-dimethyl	1.17	ca. 200	inter- mediate	>12.0	1-12 (14)	
54.1	xxv	CH ₂ CH ₂	2'-Acetoxy-5,9-dimethyl	0.19	169	low		0.5-32 (15)	
34.5 52.21 34.2	XX XXV XX	CH₃ CH₂CH≕C(CH₃)₂ CH₃	5-Ethyl-2'-hydroxy-9-methyl 5-Ethyl-2'-hydroxy-9-methyl 5,9-Diethyl-2'-hydroxy	4·9 15·9 4·2	$\begin{vmatrix} 309 \\ > 300 \\ 423 \end{vmatrix}$	low none none		2-40 (16) 0·5-16 (2) 2-60 (17)	
54.4	xxv	CH ₂ CH ₂	5,9-Diethyl-2'-hydroxy	2.1	292				
34.6	xx	CH ₃	2'-Hydroxy-9-methyl-5-propyl	2.9	>300	-			
54.5	xxv	CH ₂ CH ₂	2'-Hydroxy-9-methyl-5-propyl	0.92	>400				
42.8	XXII	CH ₃	α-2',9-Dihydroxy-5-methyl	7 9∙9	-	-			
54.9	XXVI	CH ₂ CH ₂	α-2',9-Dihydroxy-5-methyl	0.62	ca. 100	_			
42.6	XXII	CH ₃	α-9-Hydroxy-2'-methoxy-5-methyl	>100.0	>200				

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					1	Obse	rvations on	monkeys
No.	See Table	Substituent at 2	Other substituents [‡]	ED50†	LD ₅₀ †		Morphine C equiv. Dose range	
						PDC	equiv.	Dose range
54.10	XXVI	CH ₂ CH ₂	a-9-Hydroxy-2'-methoxy-5-methyl	22.2			1	1
42.9	XXII	CH ₃	α-2',9-Dihydroxy-5,9-dimethyl	6.9				
54 .11	XXVI	CH ₂ CH ₂	α-2',9-Dihydroxy-5,9-dimethyl	7.5	209		1 1	l 1

- † For explanation of these and other data see Table XIX and XX.
- (1) 60 mg/kg--Exacerbation of abstinence signs, no suppression at lower doses.
- (2) 16 mg/kg-Convulsion.
- (3) 32 mg/kg-Convulsion.
- (4) 16 mg/kg—Strong excitation accompanying suppression of abstinence signs; convulsion.
- (5) 6 mg/kg-Ataxia, increasing in severity with higher doses. 24 mg/kg-Disorientation, hallucinations.
- (6) 20 mg/kg--Sedation; sedation in normal monkeys also, not antagonized by nalorphine.
 - 30 mg/kg-Convulsion.
 - 2 mg/kg—Did not precipitate abstinence signs in non-withdrawn monkeys.
- (7) Levallorphan-like.
- (8) -No signs of toxicity reported.

- (9) 2 mg/kg-Disoriented, unable to move limb.
 - 1 mg/kg—Ptosis, relaxation of facial muscles, fixed staring pose, ataxia, excitability in non-addicted monkeys, not antagonized by nalorphine.
- (10) 30 mg/kg-Hyperirritable, exaggeration of abstinence signs, convulsion.
- (11) 24 mg/kg-Convulsion.
- (12) 2 mg/kg-Increased motor activity.
- (13) 10 mg/kg-Tremor, muscular rigidity and ataxia.
- (14) 4 mg/kg-Ataxia, increasing in severity with higher doses.
- (15) 16 mg/kg-Tremor, plus disorientation at 32 mg/kg.
- (16) 40 mg/kg-Muscular weakness, salivation, dyspnoea.
- (17) 60 mg/kg--Convulsion; some sedation but no suppression with lower doses.
- * All 5,9-dialkyl compounds belong to the a series.

No		Substituents at			Analgesic	PDC	Morphine	Min.
NO.	2'	2	5	9	ED ₅₀	FDC	equiv.	dose
10	ОН	CH ₃	CH ₃	н	10.4	none		>60.0
29.3	ОН	CH ₃	CH ₃	a-CH ₃	3.0	low	24.0	6.0
29.2	OCH ₃	CH ₃	CH ₃	a-CH ₃	9.8	low	none	10.0
50.1	OCOCH ₃	CH ₃	CH ₃	a-CH ₃	1.17	intermediate	>12.0	4.0
59†	ОН	CH ₃	CH ₃	α-CH ₃	1.69	very low	none	30.0
35.1	ОН	CH ₃	CH ₃	β -CH ₃	0.44	low	>18.0	12.0
34.2	ОН	CH ₃	C_2H_5	α-C ₂ H ₅	4·2	none		60.0
34.7	OCOCH ₃	CH ₃	C_2H_5	α -C ₂ H ₅	3.0	none		32.0
35.2	OH	CH ₃	C_2H_5	β -C ₂ H ₅	0.28	none		4.0
34.5	ОН	CH ₃	C_2H_5	α-CH ₃	4.9	low	none	40 ∙0
19.8	ОН	CH₃	C ₂ H ₅	Н	2.3	low	none	32.0
42.15	OCOCH ₃	CH ₃	CH ₃	α-OCOCH ₃	0.51	high	<u>48</u> •0	72.0
42.16	OCOCH ₃	CH ₃	CH ₃	α -OCOCH ₃ ; CH ₃	1.07	low	none	24.0
42.7	OCH ₃	CH ₃	CH_3	α -OH; CH ₃	19.7	very low	none	25.0
52.15	OH	C_5H_{11}	CH₃	α-CH ₃	2.2	low	none	16.0
52.18	OH	$CH_2CH=CH_2$	CH_3	α-CH ₃	I	none	antag.	
	OH	$CH_2CH=CH_2$	C_2H_5	a-CH3	I	none	antag.	
52.20	OH	$CH_2CH = C(CH_3)_2$	CH_3	a-CH3	I	none	antag.	
		CH ₂						
52.19	ОН	CH ₂ CH CH ₂	CH3	α-CH ₃	23.1	none	antag.	
54.7	ОН	CH ₂ CH ₂ Ph	CH ₃	н	0.48	none		16.0
54.3	ОН	CH ₂ CH ₂ Ph	CH	α-CH ₃	0.25	high	17.0	>18.0
54.2	OCH ₃	CH ₂ CH ₂ Ph	CH ₃	a-CH3	6.2	very low	none	>60.0

TABLE XXXIII. COMPARISON OF ANALGESIC EFFECTIVENESS AND PHYSICAL DEPENDENCE CAPACITY OF 6,7-BENZOMORPHANS

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TABLE XXXIII— continued

No		Substituents at			Analgesic	BDC	Morphine	Min.
INO.	2′	2	5	9	ED ₅₀	FDC	equiv.	dose
54.1 54.14 [±] 54.12 [±] 52.6 52.16 52.7 52.8	OCOCH ₃ OCH ₃ OH OH OCOC ₆ H ₄ -p-NO ₂ OH OH	$CH_{2}CH_{2}Ph$ $CH_{2}CH_{2}Ph$ $CH_{2}CH_{2}Ph$ $CH_{2}CH_{2}CH_{2}Ph$ $CH_{2}CH_{2}Ph$ $CH_{2}CH_{2}C_{6}H_{4}-p-NH_{2}$ $CH_{2}CH_{2}C_{6}H_{4}-p-OCH_{3}$	$\begin{array}{c} CH_3\\ CH_3\\ CH_3\\ CH_3\\ CH_3\\ CH_3\\ CH_3\\ CH_3\\ CH_3\\ CH_3\end{array}$	α-CH ₃ α-CH ₃ α-CH ₃ α-CH ₃ α-CH ₃ α-CH ₃ α-CH ₃	0.19 1.83 0.11 13.6 0.41 0.11 0.32	low none high none low intermediate low	none 9.0 none 0.5 none	$ \begin{array}{c} 16.0 \\ >60.0 \\ >8.0 \\ 30.0 \\ >32.0 \\ 3.0 \\ 24.0 \end{array} $
52.10 52.17#	он oco<	CH ₂ CH ₂ CH ₂ Ph	CH₃	α-CH ₃	0.055	low	none	2·0
52.3 54.8 54.13* 60.0** 34.3 35.5 34.4 71 29.4	ОН ОН ОН ОН ОН ОН ОН Н Н	$CH_2CH_2COPh \\ CH_2CH_2Ph \\ CH_2CH_2Ph \\ CH_3 \\ C$	$\begin{array}{c} CH_{3} \\ C_{2}H_{5} \\ CH_{3} \\ CH_{3} \\ C_{3}H_{7} \\ C_{2}H_{5} \\ C_{2}H_{5} \\ COOC_{2}H_{5} \\ C_{2}H_{5} \end{array}$	$\begin{array}{c} \alpha\text{-CH}_{3} \\ \text{H} \\ \alpha\text{-CH}_{3} \\ \alpha\text{-CH}_{3} \\ \alpha\text{-C}_{3}\text{H}_{7} \\ \beta\text{-CH}_{3} \\ \alpha\text{-CH}_{3} \\ \text{H} \\ \alpha\text{-C}_{2}\text{H}_{5} \end{array}$	2·3 0·16 6·6 I 71·2 0·07 1·50 10·1 5·00	none intermediate none very low none none	16-0 none	>2.0 16.0 20.0 10.0 48.0 48.0
	Morphine				2.1	high	3.0	

† Laevo-isomer of 29.3.

taevo-isomer of 54.2.

+ Laevo-isomer of 54.3.

Leavo-Isomer.

* Dextro-isomer of 54.3.

** Dextro-isomer of 29.3.

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Compound +		S	tructure	Analgesic activity	mg/kg sc.	Toxicity, LD ₅₀	mg/kg \pm S.E. #
	R ₁	R ₂	R ₃	S–W	NIH	intraven.	subcut.
W in-23,629	ОН	CH3	Br CH ₂ CH ₂ -CH ₂ -CH ₂ -CH ₂ CH ₂ -CH ₂ CH ₂ -CH ₂ CH ₂ -CH ₂ -C	22%-60; toxic at 120		7 ± 0·4	
Win-20, 740	ОН	CH₃	CH ₂ CH CH ₂ CH	25%-120	23·1 (16·7–31·9)	32 ± 3·0	310 ± 35
Win-20,836	OCH3	CH3	CH ₂ CH ₂ CH ₂ CH ₂	19%-60; toxic at 120		14 ± 0·8	ca. 222
W in-20,722	ОН	СН₃	CH ₂ COCH	I-120			
Win-23,201	ОН	CH3	CH ₂ CH ₂ CH ₂ CH ₂	I-120		24 ± 1.2	
W in-23,654	ОН	C ₂ H ₅	CH ₂ CH CH ₂ CH	I-120			

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TABLE XXXIV—continued

Compound †	Structure			Analgesic activity	mg/kg sc.	Toxicity, LD_{50} mg/kg \pm S.E.#	
	R ₁	R ₂	R ₃	S–W	NIH	intraven.	subcut.
Win-23,030	он	CH ₃	CH ₂ CH ₂ CH CH ₂ CH ₂ CH	64%-120		20 ± 1.4	ca. 160
Win-23,538	OCH₃	CH₃	CH ₂ CH CH ₂ CH ₂ CH CH ₂	27%-60		16 ± 0·9	
Win-23,100	он	C_2H_5	CH ₂ CH ₂ CH CH ₂ CH ₂ CH	Active only at toxic dose		15 ± 1.3	
Win-23,111	ОН	CH3	CH ₂ CH ₂ CH ₂ CH CH ₂ CH ₂	I-120		20 ± 1.8	
Win-24,042	ОН	CH₃	CH ₂ CH ₂ CH ₂ CH ₂ CH CH ₂ CH ₂ CH ₂ CH ₂	I-120			
Win-24,194	OCOCH₃	CH3	CH ₂ CH ₂ CH ₂ CH CH ₂ CH ₂ CH ₂				

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† The prefix Win indicates that the compound was prepared at Sterling-Winthrop Research Institute, Rensselaer, N.Y.

SKF-10,047 and SKF-9,418 were prepared at Smith, Kline and French Laboratories, Philadelphia, Pa.

FR-79 was prepared at C. H. Boehringer Sohn, Ingelheim, Germany.

We are indebted to each of these laboratories for data on the compounds.

S-W = Data on analgesic testing at the Sterling-Winthrop Research Institute. A modified D'Amour-Smith radiant heat method was used with the rat as the experimental animal. I = Inactive at dose indicated; a percentage represents that degree of increase in reaction time (normal in the 2 to 4 second range).

N.I.H. = Data from our laboratory at the National Institutes of Health. The hot plate method of EDDY and LEIMBACH⁽⁴³⁾ was used with the mouse as the experimental animal. I = Inactive at dose indicated. A specific figure is the ED₅₀ calculated by probit analysis with $1 \times SE$ limit in paratheses.

Toxicity data are those of the Sterling-Winthrop Research Institute.

Compound	AD ₅₀	(mg/kg s	c) for antag	onism of a			
Compound	vs. Phenazocine		vs. Morphine		vs. Pethidine		Antagonistic effect in monkeys
Nalorphine	0.098	(6)	0.13	(6)	0.13	(10)	Abstinence signs precipitated in morphine addicted monkeys by 0.0125 mg/kg sc and above ⁽⁸¹⁾ .
Levallorphan Win-19,631	0.046	(4)	0.058	(5)	0·052 0·047	(6) (4)	3.5 times more potent than nalorphine.
Win-19,362 NIH-7,549	0·030 0·44	(2)	0∙044 0∙027	(2)	0·049 0·019	(5)	Equivalent to levallorphan ⁽⁸²⁾ .
Win-19,797 Win-20,228	6.3	(12)	9•0	(14)	0·078 3·9	(7) (16)	Neither nalorphine-like antagonism nor morphine- like sedation at doses of 2–30 mg/kg sc no physical dependence capacity ⁽⁸²⁾ .
Win-20,264	11.0	(13)	11.6	(15)	10-9	(19)	Not definitely nalorphine-like nor morphine-like ⁽⁸³⁾ .
Win-20,548	0.033	(3)	0.048	(4)	0.018	(1)	
Win-21,021					5.1	(18)	
Win-20,992	< 1 (20–80 sc; 0.156–820 p.o.) >						
Win-21,489	}		0.19	(7)	0.094	(9)	
Win-21,490			5.8	(13)	4.2	(17)	
Win-21,287					17.0	(21)	
FR-79			Shortened of analge	duration sic			None to 6.0 mg/kg sc. No physical dependence capacity ⁽⁸²⁾ .
			effect	(18)			
Win-23,629							
Win-20,740	0.028	(1)	0.029	(1)	0.019	(2)	Equivalent to nalorphine ⁽⁸²⁾ .
Wm-20,836	0.19	(7)	0.46	(9)	0.146	(11)	
Win-20,722		10			26•0 i.p.	(22)	
Win-23,201	0.20	(8)	0.26	(8)	0.092	(8)	
Win-23,654	0.048	(5)	0.046	(3)	0.024	(3)	

TABLE XXXV. OPIATE ANTAGONISTS IN THE BENZOMORPHAN SERIES

TABLE	XXXV-	continued
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Compound	AD ₅₀ (n	ng/kg so	c) for antagon	ism of a	Antagonistic effect in monkeys		
	vs. Phenazocine		vs. Morphine			vs. Pet	hidine
Win-23,030	0.40	(9)	0.60	(11)	0.37	(13)	
Win-23,538	5-2 (slight)	(11)	0.625-40 (slight)	(17)	1.25	(15)	
Win-23,100	1.0	(10)	0.63	(12)	0.45	(14)	
Win-23,111			0.5	(10)	0.28	(12)	
Win-24,142 Win-24,194	29.0	(14)	18.0	(16)	14.5	(20)	
	1		<u> </u>		1		

 † AD₅₀ = The amount required to reduce the effect of a standard dose of analgesic by 50 per cent. The standard doses of the three analgesics were: Phenazocine \cdot HBr 0.5 mg/kg; morphine \cdot H₂SO₄ 15 mg/kg; and pethidine \cdot HCL 60 mg/kg sc. The method of measuring analgesic activity was the same as described under S-W in footnote, Table XXXIV. The tests were performed at the Sterling-Winthrop Laboratories. The figure in parentheses is the rank order of antagonistic action.

References

- 1. J.M.GULLAND and R.ROBINSON, Mem. Manchester Phil. Soc. 69, 79 (1925).
- 2. N.B. EDDY, H.HALBACH and O.J. BRAENDEN, Bull. World Health Organ. 17, 569 (1957).
- 3. A. BURGER, Med. Chem. 2nd Ed., Interscience, p. 311 (1960).
- 4. E.L. MAY and J.G. MURPHY, J. Org. Chem. 20, 1197 (1955).
- 5. E.L. MAY and J.G. MURPHY J. Org. Chem. 20, 257 (1955).
- 6. J.A. BARLTROP, J. Chem. Soc. p. 399 (1947).
- 7. N.B.EDDY, J.G. MURPHY and E.L. MAY, J. Org. Chem. 22, 1370 (1957).
- 8. J.G. MURPHY, J.H. AGER and E.L. MAY, J. Org. Chem. 25, 1386 (1960).
- 9. E. M. FRY and E. L. MAY, J. Org. Chem. 26, 2592 (1961).
- 10. S. SAITO and E. L. MAY, J. Org. Chem. 27, 948 (1962).
- 11. J. H. AGER, S. E. FULLERTON and E. L. MAY, J. Med. Chem. 6, 322 (1963).
- 12. E.L. MAY, J. Org. Chem. 22, 593 (1957).
- 13. E.L. MAY and E.M. FRY, J. Org. Chem. 22, 1366 (1957).
- 14. E.L. MAY and J.H. AGER, J. Org. Chem. 24, 1432 (1959).
- 15. J.H. AGER and E.L. MAY, J. Org. Chem. 27, 245 (1962).
- 16. S.E. FULLERTON, J.H. AGER and E.L. MAY, J. Org. Chem. 27, 2554 (1962).
- 17. S.E. FULLERTON, E.L. MAY and E.D. BECKER, J. Org. Chem., 27, 2144 (1962).
- 18. N.B.EDDY, H.HALBACH and O.J.BRAENDEN, Bull. World Health Organ. 14, 353 (1956).
- 19. E.L. MAY, H. KUGITA and J.H. AGER, J. Org. Chem. 26, 1621 (1961).
- 20. E.L. MAY and H.KUGITA, J. Org. Chem. 26, 188 (1961).
- 21. C.Schöpf and F.Borkowsky, Ann. 452, 249 (1927).
- 22. E. M. FRY, J. Org. Chem. 22, 1710 (1957).
- 23. U.WEISS, J. Amer. Chem. Soc. 77, 5891 (1955).
- 24. T.B.ZALUCKY and G.HITE, J. Med. Pharm. Chem. 3, 615 (1961).
- 25. H.KUGITA and E.L.MAY, J. Org. Chem. 26, 1954 (1961).
- 26. S. SAITO and E.L. MAY, J. Org. Chem. 26, 4536 (1961).
- 27. S. SAITO and E. L. MAY, J. Org. Chem. 27, 1087 (1962).
- 28. J. WEIJLARD, P.D. ORAHOVATS, A.P. SULLIVAN Jr., G. PURDUE, F.K. HEATH and K. PFISTER 3rd. J. Amer. Chem. Soc. 78, 2342 (1956).
- 29. A. GRÜSSNER, J. HELLERBACH and O. SCHNIDER, Helv. Chim. Acta, 40, 1232 (1957).
- 30. N.B. EDDY, H. BESENDORF and B. PELLMONT, Bull. on Narcotics, 10, 23 (1959).
- 31. T.D. PERRINE and N.B. EDDY, J. Org. Chem. 21, 125 (1956).
- 32. P.A.J.JANSSEN and N.B.EDDY, J. Med. Pharm. Chem. 2, 31 (1960).
- 33. E. L. MAY and N. B. EDDY, J. Org. Chem. 24, 1435 (1959).
- 34. E.L.MAY, J. Org. Chem. 21, 899 (1956).
- 35. J.H.AGER and E.L.MAY, J. Org. Chem. 25, 984 (1960).
- 36. E. M. FRY and E. L. MAY, J. Org. Chem. 24, 116 (1959).
- 37. M.GATES and W.G.WEBB, J. Amer. Chem. Soc. 80, 1186 (1958).
- 38. A.H. BECKETT and P. ANDERSON, J. Pharm. and Pharmacol. 228T (1960).
- 39. H. KUGITA, S. SAITO and E. L. MAY, J. Med. Pharm. Chem. 5, 357 (1962).
- 40. J.H.AGER, S.E. FULLERTON, E.M. FRY and E.L. MAY, J. Org. Chem. 28 (1963).
- 41. M. GORDON, J.J.LAFFERTY, D.H. TEDESCHI, B.M. SUTTON, N.B.EDDY and E.L. MAY, J. Med. Pharm. Chem. 5, 633 (1962).

- 42. S. ARCHER, N. F. ALBERTSON, L. S. HARRIS, A. K. PIERSON, J. G. BIRD, A. S. KEATS, J. TEL-FORD and C. N. PAPADOPOULOS, *Science*, 137, 541 (1962); S. ARCHER, N.F. ALBERTSON, L.S. HARRIS, A.K. PIERSON and J.G. BIRD, *J. Med. Chem.* 7, 123 (1964).
- 43. N.B. EDDY and D.G. LEIMBACH, J. Pharmacol. Exp. Therap. 107, 385 (1953).
- 44. C.A.WINTER, P.D. ORAHOVATS and E.G. LEHMAN, Arch. internat. Pharmacod. Therap. 110, 186 (1957).
- 45. N.B.EDDY, H.BESENDORF and B.PELLMONT, Bull. on Narcotics, 10, No.4, 23 (1958).
- 46. H. HALBACH and N.B. EDDY, Bull. World Health Organ. 28, 139.
- 47. E. L. MAY and N. B. EDDY, J. Org. Chem. 24, 294 (1959).
- 48. J.E.ECKENHOFF, Anesthesiology, 20, 355 (1959).
- 49. S. L. WALLENSTEIN, A. ROGERS and R. W. HOUDE, Pharmacologist, 1, 78 (1959).
- 50. M.S.SADOVE and M.J.SCHIFFRIN, Cur. Therap. Res. 1, 109 (1959).
- 51. T. J. DEKORNFELD and L. LASAGNA, Anesthesiology, 21, 159 (1960).
- R.W.HOUDE, S.L. WALLENSTEIN and A.ROGERS, Committee on Drug Addiction and Narcotics, National Research Council, National Academy of Sciences, Minutes of twenty-first meeting, *Addendum* 3, p. 18 (1960).
- 53. H. WENDEL, I. SHEMANO and S. D. Ross, Pharmacologist, 1, 78 (1959).
- 54. I. SHEMANO, H. WENDEL and S. D. Ross, J. Pharmacol. Exp. Therap., 132, 258 (1961).
- 55. D.H. TEDESCHI, R.E. TEDESCHI and E.J. FELLOWS, Pharmacologist, 1, 78 (1959).
- 56. D.H.TEDESCHI, R.E.TEDESCHI and E.J.FELLOWS, J. Pharmacol. Exp. Therap., 130, 431 (1960).
- 57. C.B. CARTER and N.A. DAVID, Fed. Proc. 19, 271 (1960).
- 58. C.B. CARTER and N.A. DAVID, Toxicol. and Appl. Pharmacol. 2, 564 (1960).
- 59. J.W.BELLVILLE, S.L.WALLENSTEIN, R.W.HOUDE and W.S.HOWLAND, Anesthesiology, 21, 90; Committee on Drug Addiction and Narcotics, National Research Council, National Academy of Sciences, Minutes of twenty-first meeting, Addendum 3, p.28 (1960).
- 60. J.E.ECKENHOFF, M.HELRICH and J.D.HEGE, Anesthesiology, 17, 66 (1956).
- 61. E.M.GREISHEIMER, L.W.KRUMPERMAN, B.F.RUSY and D.W.ELLIS, Anesthesiology, 21, 370 (1960).
- 62. R.BERKOWITZ, T. RODMAN and H.P. CLOSE, J. Amer. Med. Ass. 176, 1092 (1961).
- 63. C.N. PAPADOPOULOS and A.S. KEATS, Clin. Pharmacol. and Therap. 2, 8 (1961).
- 64. I.P. MCEWAN, Brit. Med. J. 2, 1763 (1961).
- C.R.STEPHEN and R.MACMILLAN, Committee on Drug Addiction and Narcotics, National Research Council, National Academy of Sciences, Minutes of twenty-first meeting, *Addendum* 3, p.43 (1960).
- 66. B.J.CILIBERTI, P.SHROFF and N.B.EDDY, Bull. on Narcotics. 16, No. 2,1 (1964).
- 67. B.P.LUSTGARTEN, S.FISCH and A.C.DEGRAFF, Fed. Proc. 19, 121 (1960).
- 68. S. L. WALLENSTEIN, R. W. HOUDE, J. W. BELLVILLE and G. N. WALD, Committee on Drug Addiction and Narcotics, National Research Council, National Academy of Siences, Minutes of twenty-first meeting, *Addendum* 3, p. 35 (1960).
- 69. S.J. PREVOZNIK and J.E. ECKENHOFF, Surg. Gynec. Obstet. 110, 669 (1960).
- E.LEAR, R.SUNTAG and I.M.PALLIN, New York State Medical Society, New York, May 9–12 (1960).
- 71. M.S.SADOVE, R.C.BALAGOT, J.M.BRANION and A.J.KOBAK, Obstet. Gynec., 16, 448 (1960).
- 72. J.D.CORBIT, Jr. and S.E.FIRST, Obstet. Gynec. 18, 488 (1961).
- 73. F. F. SNYDER, Committee on Drug Addiction and Narcotics. National Research Council, National Academy of Sciences, Minutes of twenty-first meeting, *Addendum* 3, p.1 (1960).
- 74. J.A.YOUNG, R.B.N.BROWN and R.M.SMITH Jr., Anesth. Analg. 40, 213 (1961).
- 75. N.A. DAVID and G.A. PORTER, Clin. Res. 8, 117 (1960).
- 76. A.A.KURLAND and F.GRUENWALD, Dis. Nerv. System, 23, No.5, May (1962).

BENZOMORPHANS

- 77. H.F. FRASER and H. ISBELL, Bull. on Narcotics. 12, No.2, p. 15 (1960).
- H.F.FRASER, D.E.ROSENBERG and H.ISBELL, Committee on Drug Addiction and Narcotics, National Research Council, National Academy of Sciences, Minutes of twenty-fifth meeting, *Addendum* 2, p.1 (1963).
- 79. M.GORDON, J.J.LAFFERTY, D.H.TEDESCHI, N.B.EDDY and E.L.MAY, *Nature*, 92, 1089 (1961).
- L.S. HARRIS and A.K. PIERSON, Committee on Drug Addiction and Narcotics, National Research Council, National Academy of Sciences, Minutes of twenty-fourth meeting, *Addendum* 1 (1962).
- 81. R.H.BURNS, D.A.MCCARTHY, G.A.DENEAU and M.H.SEEVERS, Fed. Proc. 17, 355 (1958).
- 82. G.A.DENEAU and M.H.SEEVERS, Committee on Drug Addiction and Narcotics, National Research Council, National Academy of Sciences, Minutes of twenty-fourth meeting, *Addendum* 2, p.15 (1962a).
- G.A.DENEAU and M.H. SEEVERS, Committee on Drug Addiction and Narcotics, National Research Council, National Academy of Sciences, Minutes of twenty-fourth meeting, *Addendum* 2, p. 16 (1962).
- 84. L. LASAGNA and H.K. BEECHER, J. Pharmacol. Exp. Therap. 112, 356 (1954).
- 85. A.S. KEATS and J. TELFORD, J. Pharmacol. Exp. Therap. 117, 190 (1956).
- 86. A.S. KEATS and J. TELFORD, J. Pharmacol. Exp. Therap. 143, 149 (1964).
- 87. H. F. FRASER and D. E. ROSENBERG, J. Pharmacol. Exp. Therap. 143, 157 (1964).

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